Review

Development of Environmentally Benign Organometallic Catalysis for Drug Discovery and Its Application

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We have developed a novel organometallic catalysis and applied it to drug discovery. Two new catalysts were found, ruthenium hydride with a nitrogen-containing heterocyclic carbene (A) and an organopalladium catalyst supported on a sulfur-terminated semiconductor, gallium arsenide (001) (B). Both catalysts are environmentally benign, because A can yield indole derivatives with good atom economy, and B can catalyze the Mizoroki–Heck reaction more than 10 times with only trace amounts of leached palladium (ppb level). We also describe our synthetic study of nitrogen-containing heterocycles using ring-closing metathesis (RCM), such as chiral bicyclic lactams, azacycloundecenes, axially chiral macrolactams, 1,2-dihydroquinolines and indoles, including the development of silyl-enol ether ene metathesis, selective isomerization of terminal olefin, enamide metathesis and cycloisomerization and its application to the syntheis of 4 natural products, (−)-coniceine, (*S*)-pyrrolam A, angustureine, and fistulosin.

Key words organometallic; green chemistry; heterocycle; ruthenium; palladium

Organometallic catalyzed carbon–carbon bond formations are now essential in organic chemistry and have been widely applied to medicinal chemistry, process chemistry, *etc.* We developed a novel organometallic catalysis and their application to drug discovery and found two new catalysts, ruthenium hydride with a nitrogen-containing heterocyclic carbene (**A**) and an organopalladium catalyst supported on a sulfur-terminated semi-conductor, gallium arsenide (001) (**B**) (Chart 1). Both catalysts are environmentally benign, because **A** can yield indole derivatives with good atom economy, and **B** can catalyze the Mizoroki–Heck reaction more than 10 times with only trace amounts of leached palladium (ppb level). In this review, we describe the development of these catalysts and their application to the synthesis of bioactive natural products.

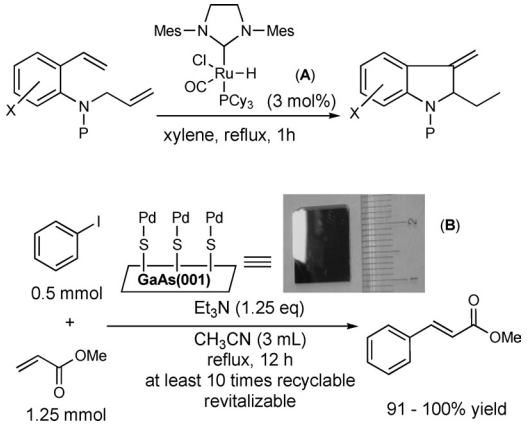

Chart 1. Our New Environmentally Benign Catalysts

1. Development of Synthetic Method for Nitrogen-Containing Heterocycles Using Ruthenium Catalyst Including A

1.1. Ruthenium Carbene Catalysts Transition metal-catalyzed olefin metathesis is an important topic in current chemistry. In this field, ruthenium carbene catalysts have received much attention and are frequently used in the synthesis of biologically active natural products, because of their stability, functional group tolerance, easy handling and commercial availability.[1—4] Over the past decades, well-defined ruthenium catalysts have been developed and Grubbs *et al.* reported the first practical catalyst (**D**).[5,6] The recent introduction of catalysts (**E**,[7—9] **G**[10]) bearing *N*-heterocyclic carbene (NHC) ligand has led to much higher reactivity (Fig. 1). For more than ten years, we have been exploring a synthetic methodology for nitrogen-containing heterocycles using these ruthenium carbene catalysts and applying them to the

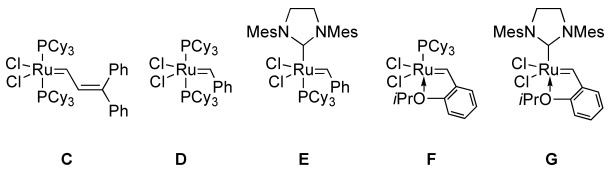

Fig. 1. Ruthenium Catalysts

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synthesis of biologically active natural products.[11—30)]

Here, we describe our synthetic study of nitrogen-containing heterocycles using ring-closing metathesis (RCM), such as chiral bicyclic lactams, azacycloundecenes, axially chiral macrolactams, 1,2-dihydroquinolines and indoles, including the development of silyl-enol ether ene metathesis and selective isomerization of terminal olefin, and its application to the synthesis of the natural products, (−)-coniceine, (*S*)-pyrrolam A and angustureine.

1.1.1. Chiral Bicyclic Lactams, Synthesis of (−)-Coniceine and (*S*)-Pyrrolam A[11,15)]: Biologically active alkaloids having an azabicyclic framework are abundant in nature. The pyrroloazocine, pyrroloazepine, quinolizidine, and indolizidine alkaloids fall into this category and have attracted considerable attention from the synthetic viewpoint due to their biological activity.[31—35)] As a part of our program[12,36—40)] directed toward the synthesis of manzamine A (Fig. 2), RCM strategy for the construction of optically active 1,2-cyclooctanopyrrolidine corresponding to the CD ring in manzamine A and related azabicycles was investigated. We studied RCM of chiral dienes which are readily available from L-proline.

The overall procedure consisted of the RCM reaction of chiral dienes (**1**—**5**) in the presence of catalyst (**C**, **D**) to form the corresponding bicyclic lactam (**6**—**9**) (Table 1). Dienes **1**—**5** were prepared from L-proline in good yield and subjected to RCM. RCM reaction of these dienes is quite interesting, since the expected azabicyclic compounds offer tremendous utility as reaction intermediates in organic synthesis. When **1** was treated with 5 mol% of catalyst **C** in degassed benzene (20 mM) at room temperature for 3 d, indolizidine **6** was obtained in 93% yield (entry 1). The reaction of **1** using catalyst **D**, on the other hand, proceeded more rapidly and **6** was obtained in 66% yield (entry 2). Cyclization of **2** to **7** also proceeded more rapidly using catalyst **D** and **7** was obtained in 73% yield, respectively (entry 3).

Initial attempts to cyclize diene **3** to 5 membered lactam **8** under similar conditions (20 mM, room temperature) using 10 mol% of **C** in benzene were unsuccessful, perhaps due to the formation of stable chelated species. Accordingly, we carried out RCM of **4** and the expected cyclization to **8** was found to occur under a forced condition (50 °C) to give (*S*)-pyrrolam A (**8**) in 30% yield (entry 4). The low yield observed in the formation of **8** appeared to be due to the instability of the product under reaction conditions.

Our next stage was to explore the feasibility of construc-

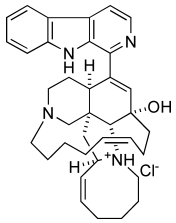
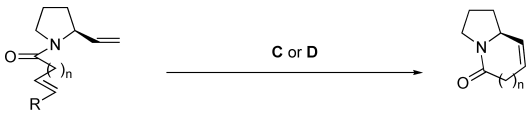


Fig. 2. Structure of Manzamine A

Table 1. Construction of Chiral Cycloalkanopyrrolidines Using RCM



1: n = 1, R = H
2: n = 2, R = H
3: n = 0, R = H
4: n = 0, R = Me
5: n = 3, R = H

6: n = 1
7: n = 2
8: n = 0
9: n = 3

Entry	Diene	Ru catalyst (mol%)	Solvent	Conc. (mM)	Temp. (°C)	Time	Yield product (%)
1	**1**	**C** (5)	Benzene	20	rt	3 d	**6**, 93
2	**1**	**D** (5)	Benzene	20	rt	18 h	**6**, 66
3	**2**	**D** (5)	Benzene	20	rt	4 d	**7**, 73
4	**4**	**D** (5)	Benzene	20	50	3 h	**8**, 30
5	**5**	**D** (25)	CH_2Cl_2	2	50	20 h	**9**, 45

Mitsuhiro Arisawa was born in 1971 in Osaka. He received his bachelor's degree (Prof. Mikio Yamazaki) in 1994 and his master's degree in 1996 (Prof. Masako Nakagawa) from the Faculty of Pharmaceutical Sciences at Chiba University, Japan. He received his Ph.D. degree from the Graduate School of Pharmaceutical Sciences of Osaka University, Japan, in 1999 (Prof. Yasuyuki Kita). He joined the Faculty of Pharmaceutical Sciences at Chiba University, Japan, in 1999 as an assistant professor. From 2002 to 2004, he spent 16 months as a visiting scholar at Harvard University, U.S.A. (Prof. Matthew D. Shair). Since 2005, he has been an associate professor of the Graduate School of Pharmaceutical Sciences at Hokkaido University, Japan. His current research interest is in organic chemistry toward the development of medicinal chemistry. In 2007, he received the Pharmaceutical Society of Japan Award for a Young Chemist.

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tion of a medium ring such as **9**, which corresponds to the CD ring in manzamine A. Although in many cases acyclic ring closure did not proceed effectively in the 8 membered series, several groups[41—45] have succeeded in obtaining an 8 membered ring system by RCM methodology. In our preliminary investigation, the cyclization of a diene, **5**, to an 8 membered ring system was not successful. However, heating the reaction of **5** and **D** (25 mol%) at 50 °C gave **9** in 45% yield (entry 5). Lactam **6** was successfully converted to (−)-coniceine (**11**), the simplest indolizidine alkaloid *via* stepwise reductions as shown in Chart 2.

1.1.2. Azacycloundecenes, toward Manzamine C, and Their Oxoanalogues[13]: Manzamine C (**12**, Fig. 2) is the simplest congener and bears an unprecedented azacycloundecene ring.[46] The total synthesis of **12** was first achieved by Hino's group[47,48] and afterward by Gerlachs' group[49] and Langlois' group[50] using their own original methods. In our synthesis of **12** and *trans*-manzamine C (**13**), *cis* and *trans* azacycloundecenes were key intermediates, and were prepared by conventional methods. We have also successfully developed an efficient synthetic route to the saturated congener **14** to determine the structure–activity relationship.[51] Manzamine C (**12**), despite its rather simple structure, shows some of the cytotoxic activity found in manzamine A. Therefore, the synthesis of **12** and related analogues is attractive from the perspective of the structure–activity relationship.

The formation of 11-membered rings by RCM is distinctly unusual.[4] Gesson and co-workers successfully applied RCM to 11-membered lactones from carbohydrate derivatives.[52] As shown in Chart 3, azacycloundecene compounds (**16** or **17**), which are key intermediates in our syntheses of **12** and **13**, were prepared by cyclization of the ditosylates **15** derived from the corresponding alkyne. To investigate an alternate convenient method for the synthesis of **16** or **17**, we studied the RCM of **18**, which can be readily obtained in 83% yield by reacting *p*-toluenesulfonamide with 6-bromo-1-hexene. The results are shown in Table 2.

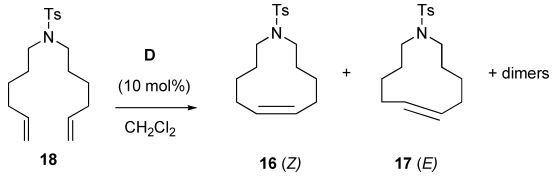
RCM with 10 mol% of the Grubbs catalyst **D** in CH_2Cl_2 (20 mM) converted **18** to a single isomer of a cyclized product (16% yield), which was identified as the *E* isomer **17** by comparison with an authentic sample prepared previously,[47,48] together with dimeric products. On the other hand, the similar reaction of **18** in diluted solution (20 mM) gave two cyclized products, **17** (major) and the *Z* isomer **16** (minor) (entry 2), which were readily separated by column chromatography. The yield was increased to 74% when the reactants were heated at 50 °C (entry 3).

We were interested in the biological activity of an oxygen-functionalized analogue (**19**, Fig. 4), which was expected to be more soluble in water. Metathesis substrate **21** was prepared from diallylation of the corresponding diol, which was obtained in 66% yield from the reaction of protected bromoethanol with *p*-toluenesulfonamide (3 steps).

Reaction of **21** in 20 mM solution of CH_2Cl_2 or benzene using 10 mol% of **D** gave dimeric compound **22** (62—67%) and *Z*-cycloundecene **20** (11—25%) (Table 3, entries 1, 2).

Under more diluted conditions, in 2 mM solution, **20** became the main product (53%, entry 3). The yield of **20** did

Table 2. RCM: Construction of Cycloundecen



Entry	Substrate conc. (mM)	Temp. (°C)	Reaction time (h)	**16** (%)	**17** (%)
1	20	rt	5.5	0	16
2	2	rt	5.5	4	50
3	2	50	2.5	12	62

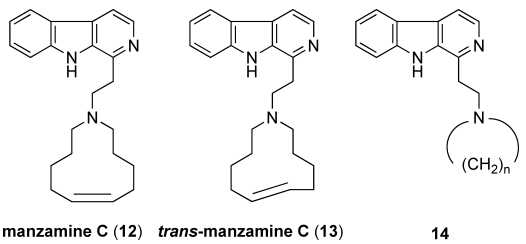


Fig. 3. Structure of Manzamine C

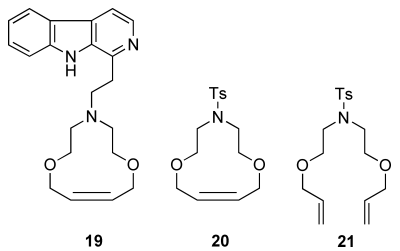


Fig. 4. Structure of Oxo-manzamine C

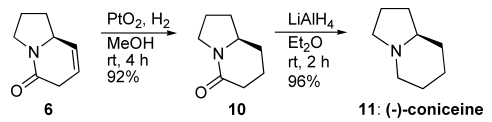


Chart 2. Synthesis of (−)-Coniceine

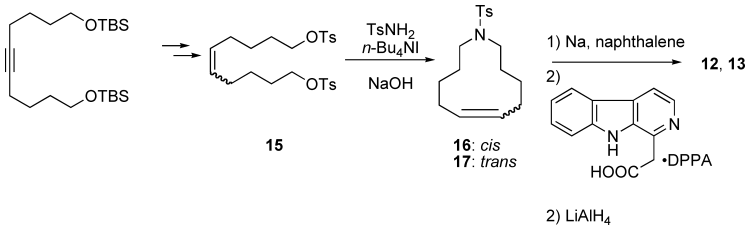


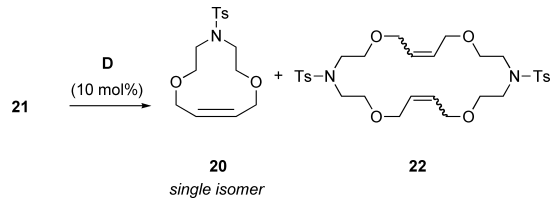
Chart 3. Synthesis of Azacycloundecene

not increase when the reaction mixture was heated. The structure of **20** was determined by X-ray analysis. In contrast to **18**, the similar reaction of **21** gave only *Z* isomer **20**, probably for conformational reasons. Thus, it is clear that RCM is an effective method for preparing oxygen-containing *Z*-undecene intermediates for manzamine C analogues, compared to the conventional method, and will be extended to the synthesis of marine alkaloids.

1.1.3. Axially Chiral Macrolactams[14,17]: We recently reported that new axially chiral ligands, 1,1′-(2,2′-bisacylamino)binaphthalenes (BINAMIDE), are effective in the ytterbium-catalyzed asymmetric Diels–Alder reaction between cyclopentadiene and crotonyl-1,3-oxazolidin-2-one (Chart 4).[53]

1,1′-(2,2′-Bisacylamino)binaphthalenes (**23**—**25**) were synthesized by reacting binaphthyldiamine with mixed anhydride of the corresponding acid, and then reacting the product with ruthenium carbene catalyst (**D**) under various conditions (Table 4).

Table 3. RCM: Construction of Oxygen Containing Cycloundecen



Entry	Solvent	Substrate conc. (mM)	Temp. (°C)	Reaction time	**20** (%)	**22** (%)
1	Benzene	20	rt	4 d	11	62
2	CH_2Cl_2	20	rt	15 h	25	67
3	CH_2Cl_2	2	rt	15 h	53	32
4	CH_2Cl_2	2	50	15 h	49	41

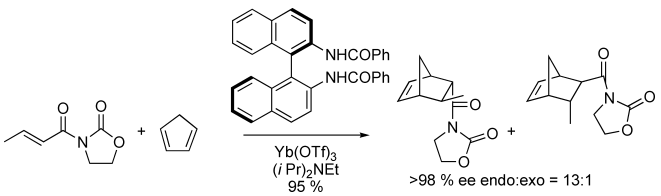


Chart 4. Diels–Alder Reaction Using Chiral BINAMIDE

Initial experiments were conducted on **23** in CH_2Cl_2 (34 mM) with Grubbs' catalyst **D** (10 mol%) at room temperature. Although the yield was low, macrolactam **26** was obtained as a single isomer, which was assigned to be *E* on the basis of its X-ray analysis. Dilution and less mild conditions (50 °C) using 30 mol% of **D** provided the best yield (96%) of **26** (entry 2).

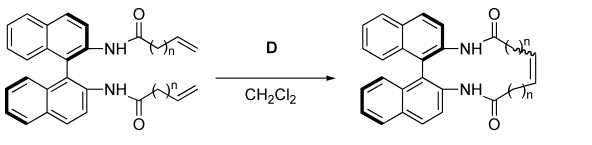
When RCM of 5-hexenoyl derivative **24** was carried out under similar reaction conditions, a remarkably different behavior was observed with regard to the reaction time and the products. The reaction proceeded more rapidly and a mixture of *E* and *Z* geometric isomers **27** was obtained in 63% yield, favoring the *Z* isomer in contrast to **23**, which could be separated by silica gel chromatography (entry 3). Dilution of the reaction mixture increased the yield of **27** to 89% (entry 4). RCM of **24** occurs most efficiently in CH_2Cl_2 at refluxing temperature using 5 mol% of **D** (entry 5).

Starting with 6-heptenoyl amide **25**, under similar conditions, the 18-membered macrolactam **28** was also obtained as a mixture of *E* and *Z* isomers (entry 6). In this reaction, the *E* isomer was mainly obtained.

It is generally recognised that one of the major problems in ring-closing ene–ene metathesis is how to control/predict the stereoselectivity in the formation of the new double bond.[54—64] In the RCM of dienes **23** and **25** to the 14-membered lactam **26** and the 18-membered lactam **28**, *E*-isomers are the major products. On the other hand, the RCM of **24** to the 16-membered ring lactam **27** gave a *Z*-isomer as the major product (Table 4).

As shown in Chart 5, a stereocontrolled RCM product (**30**) might be useful as a key intermediate for chiral ligands, while the symmetric dicarboxylic acid (**31**) is a typical metabolite of patients who lack medium acyl CoA dehydrogenase.[65] To the best of our knowledge, the preparation of **31**, which might be used as a building block for biologically active natural products, has not yet been reported. Although it is not yet clear what factors control the stereoselectivity, we studied the RCM reactions of tethered *di*-hexenoyl derivatives under various conditions (*i.e.*, with various solvents, catalysts, and templates) and examined the stereoselectivity of the reaction leading to the new double bond. Among these conditions, the selection of a template was found to be the most effective way to influence stereoselectivity and that the

Table 4. RCM of Bisacylamino Binaphthalenes



Entry	Substrate	**D** (mol%)	Conc. (mM)	Temp. (°C)	Time (h)	Product	Yield (%)	
1	**23**	10	34	rt	18	**26**	14	*E* only
2	**23**	30	11	50	15	**26**	96	*E* only
3	**24**	30	11	50	2.5	**27**	63	*E*/*Z*=1/2.0
4	**24**	30	1	50	2	**27**	89	*E*/*Z*=1/2.1
5	**24**	5	6	50	2.5	**27**	94	*E*/*Z*=1/2.5
6	**25**	5	7	50	6	**28**	90	*E*/*Z*=4.7/1

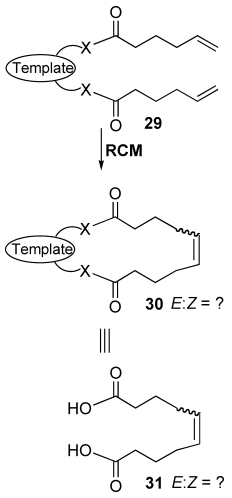


Chart 5. Synthesis of *Di*-hexenoyl Derivatives

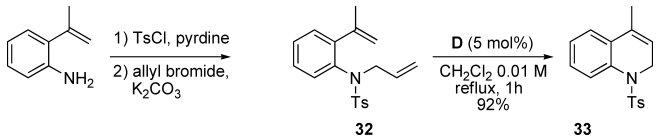


Chart 6. Synthesis of 1,2-Dihydroquinoline Using RCM

desired isomer could be obtained as a major product.

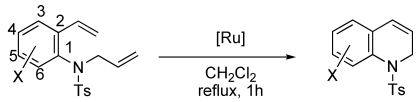
These structures of cyclized macrolactams are quite novel and have a unique axial angle compared to the corresponding precursors, which would be expected to make them useful for asymmetric reactions.

1.1.4. 1,2-Dihydroquinolines: Quinoline is a major class of alkaloid and plays an important role in the fields of natural products and medicinal chemistry. Several methods for synthesizing quinoline have been known since the late 1800s. However, despite their versatility, these conventional methods have several drawbacks. First, these reactions usually require high temperature and/or strongly acidic conditions, which leads to the decomposition of products and a tedious isolation procedure. Regioselectivity is another problem with the intramolecular electrophilic substitution of unsymmetrically substituted aniline derivatives. To overcome these problems, modern synthetic methods for quinoline using a transition metal-catalyst, such as ruthenium, palladium, rhodium, iron, copper, manganese or cobalt, have been investigated.[66—86]

In our continuing study of the RCM reaction and our approaches to the synthesis of novel antimalarial agents,[87] we developed a novel method for synthesizing substituted 1,2-dihydroquinolines using ene–ene metathesis and silyl or alkyl enol ether–ene metathesis, which proceeds under mild conditions and gives an excellent yield. This process leads to spontaneous air oxidation to quinoline after deprotection. We also describe its application to the synthesis of key intermediates for antimalarial agents, such as quinine, chloroquine, and PPMP-quinine hybrid and total synthesis of augustureine.

We first investigated RCM conditions for α,ω-diene **32** derived from commercially available 2-isopropenylaniline (Chart 6). When **32** was reacted with 5% of catalyst **D** in CH_2Cl_2 at refluxing temperature for 1 h, the corresponding 1,2-dihydroquinoline **33** was obtained in 92% yield.

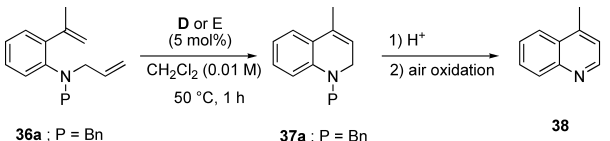
Table 5. Synthesis of 1,2-Dihydroquinoline Using RCM



34a: H, **34b**: 6-OMe, **34c**: 5-OMe
34d: 4-OMe, **34e**: 3-OMe
34f: 4,5,6-triOMe, **34g**: 6-Cl
34h: 5-Cl, **34i**: 4-Cl, **34j**: 3-Cl
34k: 3-Me, **34l**: 6-Me

Entry	Substrate	[Ru]	Yield (%)
1	**34a**	**D**	93
2	**34b**	**D**	100
3	**34c**	**D**	90
4	**34d**	**E**	95
5	**34e**	**D**	74
6	**34f**	**E**	90
7	**34g**	**D**	87
8	**34h**	**D**	100
9	**34i**	**E**	90
10	**34j**	**D**	100
11	**34k**	**D**	95
12	**34l**	**D**	100

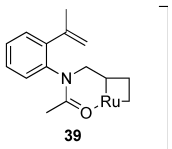
Table 6. Effect of Protective Groups on Nitrogen



36a ; P = Bn
b ; P = Ac
c ; P = Boc

37a ; P = Bn
b ; P = Ac
c ; P = Boc

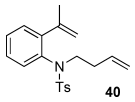
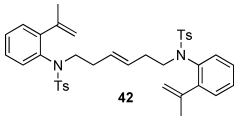
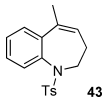
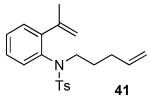
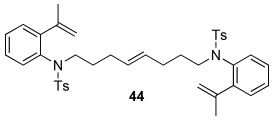
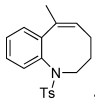
Entry	Substrate	Ru-catalyst	Product **38** (%)
1	**36a**	**D**	95
2	**b**	**D**	0
3	**b**	**E**	98
4	**c**	**D**	63
5	**c**	**E**	97



We examined the scope and limitations of RCM for 1,2-dihydroquinoline synthesis. Various dienes were prepared from anthranilic acid derivatives and subjected to RCM reaction. The results are summarized in Table 5.

The reaction of **34a**—**l** with **E** (5 mol%) in refluxing CH_2Cl_2 for 1 h gave the corresponding 1,2-dihydroquinolines (**35a**—**l**) *via* RCM in good to excellent yields (Table 5) regardless of the substituents (methoxy, chloro or methyl) on the aromatic ring. Having established the RCM conditions, we next examined the effect of protecting groups on nitrogen. Dienes **36a**—**c**, which were readily prepared from commercially available *o*-aminostyrene, were reacted with both catalysts **D** and **E**. The reaction of *N*-benzyl derivative **36a** with catalyst **D** gave **37a** in excellent yield (Table 6, entry 1), while *N*-acetyl derivative **36b** did not give the desired cyclized product (entry 2). In this case, catalyst **E** probably reacted with the terminal double bond in **36b** to form the chelated intermediate **39**, which prohibited further RCM. When *N*-*tert*-butoxycarbonyl derivative **36c** was treated with catalyst **D** under similar conditions, 1,2-dihydroquinoline **37c** was obtained in modest yield. On the other hand, with catalyst **E**, the yields of **36b** and **36c** dramatically increased

Table 7. Effect of Ru-Catalysts on the RCM of Dienes **40** and **41**

Entry	Substrate	Ru-catalyst	Product	Yield (%)
1	 **40**	**D**	 **42**	100
2		**E**	 **43**	100
3	 **41**	**D**	 **44**	95
4		**E**	 **45**	99

to give **37b** and **37c**, respectively, in almost quantitative yields (entries 3, 5). The protective groups on nitrogen of products **37a**—**c** were readily removed during silica gel column chromatography to give 1,2-dihydroquinolines, which were spontaneously oxidized to give 4-methylquinoline **38** quantitatively.

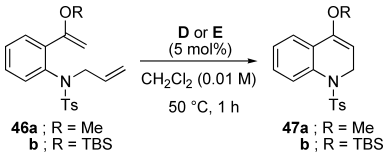
We next investigated a similar RCM for medium-sized rings such as in benzoazepine and benzoazocine. Dienes **40** and **41** were subjected to the above reaction conditions using both Grubbs' catalysts (**D**, **E**). The reaction of **40** and **41** in the presence of catalyst **D** gave only the dimeric products **42** and **44**, respectively. In sharp contrast, the corresponding benzoazepine **43** and benzoazocine **45** were obtained with catalyst **E** in excellent yields (Table 7). Isolated **42** and **44** were converted to **43** (5 h, 98%) and **45** (6 h, 97%), respectively, under the same conditions using catalyst **E**.

1.1.4.1. Silyl enol ether–ene metathesis[16]: Many quinoline alkaloids which show important bioactivities, such as quinine and chloroquine, contain substituents at the 4-position. Therefore, we next focused our attention on extending this reaction to the synthesis of 4-substituted quinolines. For this purpose, we studied the synthesis of 4-methoxy- and 4-siloxy-1,2-dihydroquinolines, which, in turn, could be converted to various 4-substituted quinolines, using ene–enol ether metathesis (Table 8).

Enol methyl ether **46a** and enol silyl ether **46b** were prepared from commercially available *o*-aminoacetophenone and subjected to our reaction conditions using catalysts **D** and **E**, respectively. When enol methyl ether **46a** and enol silyl ether **46b** were treated with **D**, the cyclized product was not obtained at all and the starting materials were recovered (entries 1, 3). In contrast, treatment of the same substrates with catalyst **E** gave the corresponding 4-methoxy-1,2-dihydroquinoline **47a** and 4-siloxy-1,2-dihydroquinoline **47b** in 95% yield, respectively (entries 2, 4). This novel synthetic method could be applied to large-scale, multigram, syntheses.

1.1.4.2. Formal synthesis of chloroquine, chinine, PPMP-quinine hybrid[21]: Encouraged by these results, we applied this novel method to the synthesis of key intermediates of antimalarial agents, such as quinine,[88—92] chloroquine,[93,94] and PPMP-quinine hybrid,[87] which are shown in Chart 7.

Table 8. Effect of Ru-Catalyst on the Ene–Enol Metathesis of **46a** and **46b**



Entry	Substrate	Ru-catalyst	Conc. (M)	Product (%)
1	**46a**	**B**	0.01[a]	**47a** (0)
2	**a**	**C**	0.01[a]	**a** (95)
3	**b**	**B**	0.01[a]	**b** (0)
4	**b**	**C**	0.01[a]	**b** (95)
5	**b**	**C**	0.01[a]	**b** (99)
6	**b**	**C**	0.1[a]	**b** (96)
7	**b**	**C**	0.1[b]	**b** (97)

a) Degassed conditions. *b*) Without degassing.

1.1.4.3. Total synthesis of angustureine and determination of its absolute structure[24]: A novel 2-substituted quinoline alkaloid, angusturiene, was isolated from *Galipea officinalis* Hancock by Jacquemond-Collet *et al.* in 1999.[95] The same plant has been previously investigated and 5 quinoline alkaloids have already been reported by Rakotoson *et al.* in 1998.[96] Genus *Galipea* Aublet is composed of approximately 20 species including *Galipea officinalis* Hancock, a shrub indigenous to the mountains of Venezuela that is known to contain 2-substituted quinoline alkaloids. These alkaloids were formerly used in folk medicine as bitter tonic to treat dyspepsia, dysentery and chronic diarrhea, and fever.[97] The ethanolic extract from the bark of *G. officinalis*, called angostura, possesses activity against *Mycobacterium tuberculosis*.[98] Recently, the antimalarial and cytotoxic activities of angusturiene, galipeine, cuspareine and galipinine have also been reported (Fig. 5).[99]

Although the natural angusturiene is one of the main isolated fraction (980 mg from 1 kg of dried bark), its absolute configuration had not yet been reported by the time we

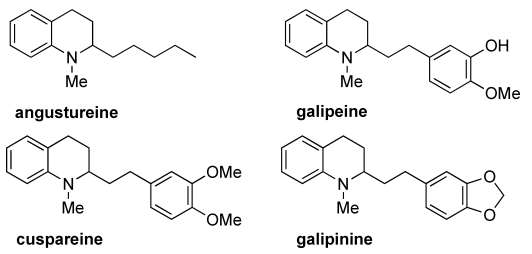


Fig. 5. Structures of 2-Substituted Quinoline Alkaloids with Anti-malarial Activity Isolated from *Galipea offinalis*

started this research project.[95] In the middle of our synthetic study, Wang *et al.* described the synthesis of angusturiene using iridium-catalyzed hydrogenation.[100] We would like to present our independent and original synthesis of optically pure (+)-(*S*)-angusturiene and determination of the absolute configuration of the natural product, angusturiene.

As shown in Chart 8, the synthesis of angusturiene began with Wittig olefination to convert readily available 2-nitrobenzaldehyde **48** to styrene **49**, followed by treatment of **49** with Zn powder in AcOH to afford aniline **50**. Tosylation of the resulting amino group proceeded to give tosylated ani-

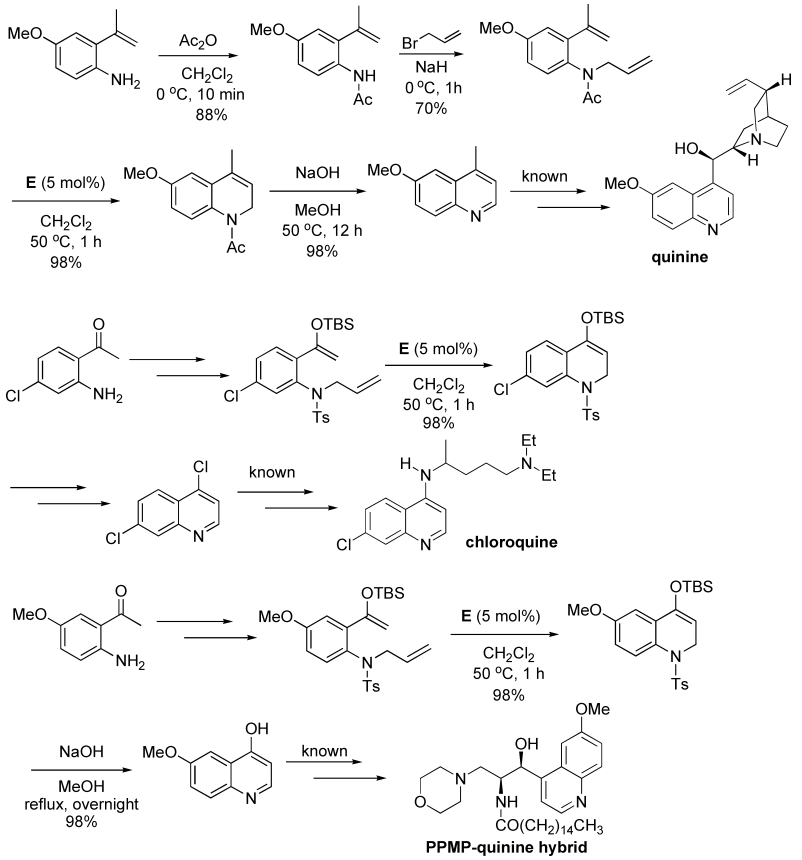
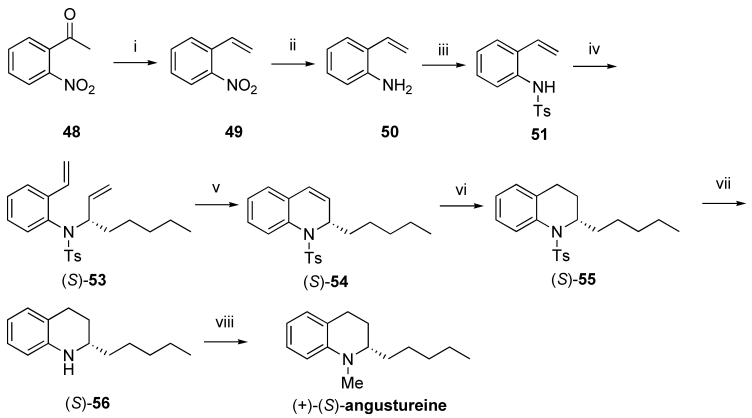


Chart 7. RCM Based Preparation of Key Intermediate for Quinine, Chloroquine and Quinine-PPMP Hybrid



(i) Ph_3PMeBr, $KN(TMS)_3$, THF, 20 °C, 1h, 90%; (ii) Zn powder, AcOH, 20 °C, 2 h, 68%; (iii) TsCl, pyridine, CH_2Cl_2, 20 °C, 1 h, 86%; (iv) (*R*)–CH_2=CH–CH(OH)–$(CH_2)_4$–CH_3 **52**, DEAD, PPh_3, THF, 20 °C, 2 h, 78%; (v) Ru catalyst **E**, CH_2Cl_2 0.01 M, 50 °C, 1 h, 92%; (vi) Pt_2O, H_2, MeOH, 20 °C, 12 h, 94%; (vii) naphthalene sodium, DME, -65 °C, 10 min, 99%; (viii) MeI, K_2CO_3, THF, 85 °C, 80%.

Chart 8. Synthesis of Angusturiene

line **51** in 86% yield.

Installation of a C-2 side chain was accomplished by employing Mitsunobu reaction as the first key step with readily available (*R*)-alcohol **52** in the presence of DEAD and PPh_3 to give the desired α,ω-diene **53** in 78% yield, 99% ee.[101] With substrate **53** in hand, RCM as the second key step was undertaken to furnish a quinoline skeleton using catalyst **E** 0.01 M in CH_2Cl_2 at 50 °C for 1 h. The corresponding 1,2-dihydroquinoline was obtained in 92% yield. Next, hydrogenation of dihydroquinoline **54** with Adam's catalyst in MeOH under H_2 atmosphere gave tetrahydroquinoline **55** in 94% yield, followed by detosylation resulting in tetrahydroquinoline **56** quantitatively. Finally, methylation of free nitrogen enabled the completion of (+)-(*S*)-angusturiene synthesis in 80% yield. HPLC analysis indicated synthesized (+)-(*S*)-angusturiene had 94% ee, $[\alpha]_D^{23}$ +7.91° (c=1.00 $CHCl_3$), $[\alpha]_D^{26}$ +4.35° (c=1.00 CH_2Cl_2); $[\alpha]_D^{26}$ +5.18° (c=1.00 MeOH); $[\alpha]_D^{26}$ +5.10° (c=1.00 EtOH), lit.[95] $[\alpha]_D$ −7.16°.

1.1.4.4. 2-Quinolinone[26]: 2-Quinolinones are valuable intermediates in organic synthesis[102] and *N*-sulfonyl-2-quinolinones are difficult to prepare by conventional methods because *O*-sulfonyl-2-quinolinones would be obtained preferentially instead of *N*-sulfonylation. In our previous work on the synthesis of dynemicin A,[103] we found that *N*-protected-2-quinolinone derivatives are good dienophiles for the Diels–Alder reaction (Chart 9). Theoretically, *N*-sulfonyl-2-quinolinones are better dienophiles than *N*-methoxycarbonyl or *N*-methoxymethyl derivatives. However, we could not prepare *N*-sulfonyl-2-quinolinones using conventional methods.

Dienes (**57**) were prepared by condensation of the corresponding *N*-protected aniline and acid chloride. When catalyst **E** was used for RCM of **57a** under the standard conditions, no cyclized product was obtained and the starting material was recovered (Table 9, entry 1). Thus, instead of catalyst **E**, catalyst **F** was used under the same reaction conditions. The *N*-tosyl-2-quinolinone **58a** was obtained in trace amounts. When the reaction temperature was raised to 100 °C, *N*-tosyl-2-quinolinone **58a** was obtained in 56% yield, while rearranged product **59** was also obtained in 32% yield (entry 3). In entry 4, the reaction temperature was reduced to 80 °C, the reaction mixture was stirred for 4 h, and the desired *N*-tosyl-2-quinolinone **58a** was obtained in quantitative yield. Thermal rearrangement of **58** to **59** occurred at 100 °C quantitatively without any catalyst. Compound **59** should be a useful substrate for the synthesis of 2-substituted quinolines by a coupling reaction.

N-Crotonoyl-*N*-tosylaminostyrene **57b** was subjected to the same reaction conditions as in entry 4 and gave *N*-tosyl-2-quinolinone **58a** in 74% yield (entry 5). RCM of **57c** was accomplished within 5 h using catalyst **F**, and *N*-benzenesulfonyl-2-quinolinone **58b** was obtained in 90% yield (entry 6).

Thus, the development of a novel method for preparing *N*-sulfonyl-2-quinolinone was achieved by RCM using a well-defined Hoveyda catalyst (**E**) and dienes at 80 °C. The reaction proceeded efficiently under mild conditions.

1.2. Ruthenium Hydride, A

1.2.1. Selective Isomerization of Terminal Olefin and Synthesis of Substituted Indole[18]: According to our findings regarding silyl enol ether–ene metathesis, we attempted the cross-metathesis of silyl enol ether with terminal olefin. Although this cross-metathesis did not succeed, we found that selective isomerization of terminal olefin ($R–CH_2–CH=CH_2$) to internal alkene ($R–CH=CH–CH_3$) took place, when 5 mol% of catalyst **E** was used together with 10 eq of vinyloxytrimethylsilane (**61a**) (Table 10). This novel isomerization is effective for monosubstituted terminal olefins (Table 11).

Indole synthesis has been the subject of intensive investigations, especially in the areas of alkaloid synthesis and medicinal chemistry.[104]

Our conditions favor isomerization rather than metathesis as a competitive reaction. This notable characteristic reaction is clearly demonstrated using *N*-allyl-*o*-vinylaniline (**34**). Through optimization of the amount of **61a** for **34a**, it became clear that 1 eq of **61a** was sufficient to convert **34a** to the enamide (**65a**) in excellent yield (Table 12). Subsequent

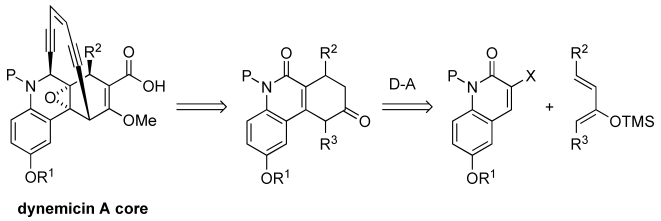
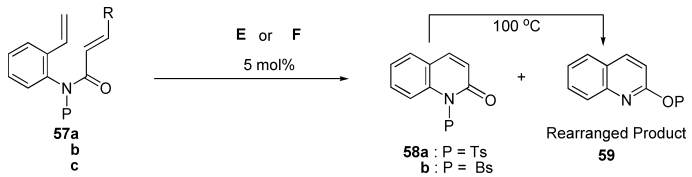


Chart 9. Diels–Alder Reaction for Dynemicin A Core

Table 9. Preparation of *N*-Sulfonyl-2-quinolinone



Entry	Substrate		Catalyst	Conditions			Product (%)	Remark
	R	P		Temp. (°C)	Solvent	Time (h)		
1	**57a** H	Ts	**E**	50	CH_2Cl_2	1	NR	—
2	**a** H	Ts	**F**	50	CH_2Cl_2	1	**58a** (trace)	—
3	**a** H	Ts	**F**	100	Toluene	4	**58a** (56)	Rearrange 32%
4	**a** H	Ts	**F**	80	Toluene	4	**58a** (95)	—
5	**b** Me	Ts	**F**	80	Toluene	4	**58a** (74)	STM 20%
6	**c** H	Bs	**F**	80	Toluene	5	**58b** (90)	—

treatment of **65a** without purification (obtained by evaporation of the solvent) with **E** (5 mol%) in refluxing benzene for 1 h gave indole (**66a**) in quantitative yield. These results provide the first example of aromatic enamide metathesis and indole synthesis using RCM. The effect of the substituent on nitrogen was examined, and the results are shown in Table 13. Not only *p*-toluenesulfonyl, but also acetyl, benzoyl, *tert*-butoxycarbonyl, benzyloxycarbonyl and methanesulfonyl derivatives gave the corresponding indoles (**66**) *via* enamides (**65**).

To clarify the scope and limitations of this indole synthesis, the effect of the substituent on the aromatic ring was examined, and the results are summarized in Table 14. Under our optimized reaction conditions, **34a**—**l** gave enamide (**65a**—**l**) quantitatively. Although substituents at the *ortho* position of styrene in **34**, such as in **34e**, **34j**, and **34k**, prevented cyclization to give the corresponding indoles (entries 5, 10, 11) probably due to steric and/or chelating effects, other substrates gave the corresponding RCM product in good to excellent yields.

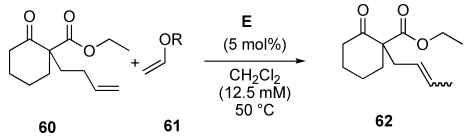
1.2.2. Synthesis of Indoline Using Cycloisomerization: After our discovery of olefin isomerization using **E**, we envisioned that the cycloisomerization of **34** might proceed at higher temperature. As shown in Table 15, the reaction of **34a** and **61a** with **E** gave **65a** exclusively (entry 1). In contrast to the reaction in CH_2Cl_2, the same reaction in refluxing xylene gave **67a** as the major product (entry 4) together with **65a**. When 10 mol% of **E** was used, the yield of **67a** increased to 81%.

The effect of the substituent at the nitrogen was examined, and the results are summarized in Table 16. Acetyl, benzoyl, *tert*-butoxycarbonyl, benzyloxycarbonyl, and methanesulfonyl derivatives gave cycloisomerized products (**67**, **68**) in yields of 69 to 99%. Sulfonamide and derivatives (**34a**, **q**) gave indoline (**67**) in excellent yields. The reaction of methanesulfonyl derivative (**34q**) with 1 mol eq of **61a** gave a mixture of **67** (71%) and 1,2-dihydroquinoline (29%), indicating that 1 eq of **61a** was not sufficient for the formation of **67**. Consequently, the yield of **67** increased up to 86% with the use of 3 eq of **61a** (entry 6).

To determine the scope and limitations of the present catalytic reactions, the substituent effect was examined using several substrates (**34a**—**l**), and selected results are shown in Table 17. All of the substrates, except **34b**, **34f** and **34g**, gave cycloisomerized products in yields of 24 to 84%. This methodology was also extended to the construction of 3-methylene-2,3-dihydrobenzofuran (**70a**—**c**). As shown in Table 18, when *O*-allyl-*o*-vinylphenol derivatives (**70a**—**c**) were refluxed in toluene with **E** and **61a**, **70a**—**c** were obtained in reasonable yields, except that **69d** gave only isomerization product in low yield and **69d** was recovered in 62% yield. The results with **34b**, **34f**, **34g** and **69d** suggest that chelation between the *o*-substituent with Ru catalyst and/or steric effects might prevent cycloisomerization.

As a further application, the cycloisomerization of a variety of *N*-functionalized alkyl-*o*-vinylanilines was examined. The reactions of **34r**, **s**, and **t** were performed with 1 eq of **61a** with **E** in refluxing xylene for 2 h (Table 19). Diene **34r** gave cycloisomerization product **67r** as the major product to-

Table 10. Reaction of **60** with Various Sily Enol Ethers and Vinyl Ethers in the Presence of Ruthenium Carbene Catalyst (**E**)

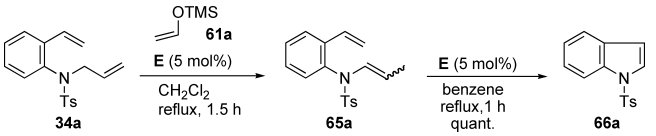


60 **61** **62**

Entry	Enol ethers R	eq	Time (h)	**62** (%)	*E*/*Z* ratio of **8**[a]
1	**61a** TMS	2	20	60	2.6/1
2	**61a** TMS	10	3	Quant.	3.5/1
3	**61b** Ac	10	23	NR	
4	**61c** Et	10	3	12	—[b]
5	**61c** Et	10	24	Quant.	3.2/1

a) The ratio were determined by ^{1}H-NMR. *b*) Not determined.

Table 12. Optimization of the Amount of **61a** for **34a**

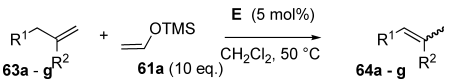


34a **65a** **66a**

Entry	**61a** (eq)	Yield of **66a** (%)
1	10	Quant.
2	5	90
3	2	96
4	1	94
5	0.1	nd[a]

a) Mixture of enamide, 1,2-dihydroquinoline and indole (0.41/0.17/1).

Table 11. Novel Isomerization of Various Terminal Olefins

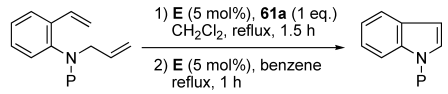


63a - g **64a - g**

Entry	Substrate	R^1	R^2	Time (h)	Yield (%)[a]	*E*/*Z*[b]
1	**63a**	Ph	H	1.5	Quant. (34)	12.8/1
2	**63b**	$PhCH_2$	H	3.0	58	2.8/1
3	**63c**	*p*-$MeOC_6H_4CH_2$	H	3.0	78	8.5/1
4	**63d**	$HO(CH_2)_3$	H	3.0	Quant. (34)	6.1/1
5	**63e**	$BnO(CH_2)_3$	H	3.0	Quant. (96)	8.2/1
6	**63f**	BnO	H	3.0	73	1/1.25
7	**63g**	$BnOCH_2$	CH_3	3.0	NR	—

a) Yields in parenthesis indicate the isolated yields. *b*) Determined by ^{1}H-NMR.

Table 13. Indole Synthesis: Substituent Effect on Nitrogen



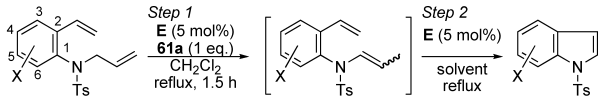
34a: Ts, **34m**: Ac, **34n**: Bz
34o: Boc, **34p**: Cbz,
34q: Ms

66

Entry	Substrate	Yield (%) **66**
1	**34a**	94
2	**34m**	82
3	**34n**	86
4	**34o**	80
5	**34p**	86[a]
6	**34q**	75

a) Reaction time of RCM was 16 h.

Table 14. Synthesis of Indole (**66**) from **34**



34a: H, **34b**: 6-OMe, **34c**: 5-OMe
34d: 4-OMe, **34e**: 3-OMe,
34f: 4,5,6-triOMe, **34g**: 6-Cl,
34h: 5-Cl, **34i**: 4-Cl, **34j**: 3-Cl
34k: 3-Me, **34l**: 6-Me

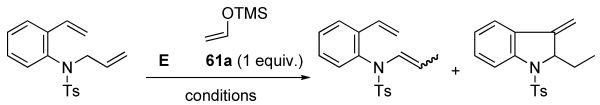
65 quant.

66

Entry	Substrate	Reaction conditions of Step 2		Product (%)	
		Solvent	Reaction time	**66**	**65**
1	**34a**	Benzene	1	94	—
2	**34b**	Benzene	1	83	—
3	**34c**	Toluene[b,c]	16	96	—
4	**34d**	Benzene	3	100	—
5	**34e**	Toluene[b,d]	32	54	46
6	**34f**	Toluene[b]	17	83	—
7	**34g**	Toluene[b]	4.5	85	—
8	**34h**	Toluene[b]	13	79	—
9	**34i**	Toluene[b]	2	86	—
10	**34j**[a]	Toluene[b]	24	33	67
11	**34k**	Toluene[b]	24	20	80
12	**34l**	Benzene	1	77	—

a) The reaction time of Step 1 was 4 h. *b*) Degassed. *c*) 10 mol% of **E** was employed. *d*) 20 mol% of **E** was employed.

Table 15. Isomerization and Cycloisomerization of Diene **34a**

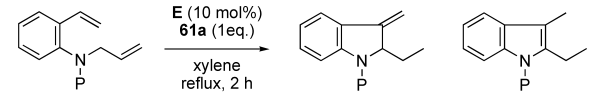


34a **65a** **67a**

Entry	**E** (mol%)	Conditions	Yield (%)[a]	
			65a	**67a**
1	5	CH_2Cl_2, reflux, 1.5 h	Quant.	0
2	5	Toluene, 40 °C, 2 h	97	3
3	5	Toluene, reflux, 2 h	65	35
4	5	Xylene, reflux, 2 h	30	68
5	10	Xylene, reflux, 2 h	12	81

a) Yields were estimated by ^{1}H-NMR spectroscopy.

Table 16. Cycloisomerization: Substituent Effect on Nitrogen



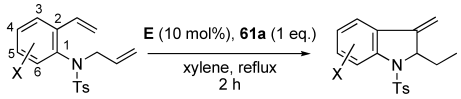
34a: Ts, **34m**: Ac, **34n**: Bz
34o: Boc, **34p**: Cbz,
34q: Ms

67 **68**

Entry	Substrate	Yield (%) **67** and **68** (ratio of **67**/**68**)
1	**34a**	81 (100/0)
2	**34m**	69 (57/43)
3	**34n**	86 (86/14)
4	**34o**	92 (84/16)
5	**34p**	99 (79/21)
6	**34q**	86[a] (100/0)

a) 3 eq of **61a** was used.

Table 17. Synthesis of Indoline from **34**



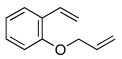
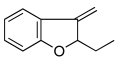
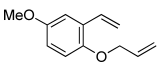
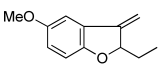
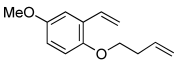
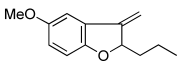
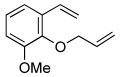
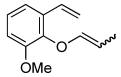
34a: H, **34b**: 6-OMe, **34c**: 5-OMe
34d: 4-OMe, **34e**: 3-OMe
34f: 4,5,6-triOMe, **34g**: 6-Cl
34h: 5-Cl, **34i**: 4-Cl, **34j**: 3-Cl
34k: 3-Me, **34l**: 6-Me

67

Entry	Substrate	Yield (%) **67**
1	**34a**	81
2	**34b**	0[a]
3	**34c**	52
4	**34d**	24
5	**34e**	63
6	**34f**	0[a]
7	**34g**	0[a]
8	**34h**	78
9	**34i**	84
10	**34j**	78
11	**34k**	95
12	**34l**	0[a]

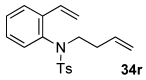
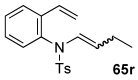
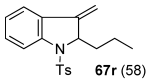
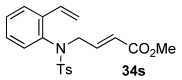
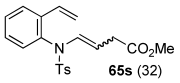
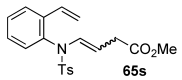
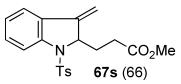
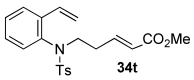
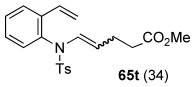
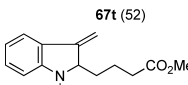
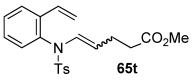
a) Enamide was obtained quantitatively.

Table 18. Cycloisomerization to Benzofuran Derivatives

Entry	Substrate	Product	Yield (%)
1	 **69a**	 **70a**	78
2	 **69b**	 **70b**	76
3	 **69c**	 **70c**	73
4	 **69d**		27[a]

Conditions: **E** (10 mol%), **61a** (1 eq), toluene, 2 h, reflux. *a*) 62% of **69d** was recovered.

Table 19. Cycloisomerizarion of Dienes

Entry	Substrate	Product (yield, %)	Recovery (%)
1	 **34r**	 **65r** (26)  **67r** (58)	
2	 **34s**	 **65s** (32)	**34s** (57)
3	 **65s**	 **67s** (66)	**65s** (21)
4	 **34t**	 **65t** (34)  **67t** (52)	
5	 **65t**	**67t** (80)	**65t** (20)

Conditions: **E** (10 mol%), **61a** (1 eq), xylene, reflux, 2 h.

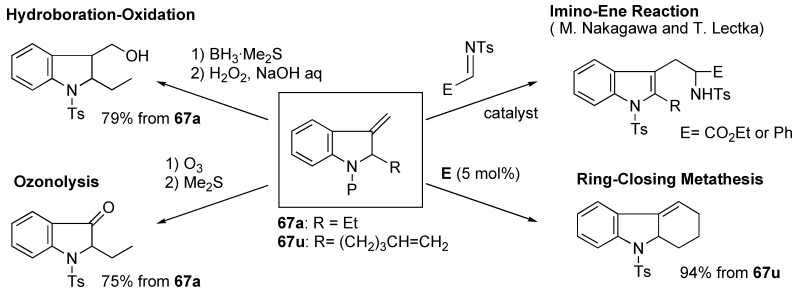


Chart 10. Reactions of 3-Methylene Group

gether with isomer **65r** (entry 1). Isomerization of **34s** gave **65s** in 32% yield together with unreacted **34s** (57%) (entry 2). Likewise, the reaction of **34t** gave **65t** and **67t** in respective yields of 34% and 52% (entry 4). When enamides (**65s**, **65t**) were subjected to the same reaction conditions, **67s** and **67t** were obtained in respective yields of 66% and 80% (entries 3, 5), which shows that enamides **65** were intermediates for **67**. The present cycloisomerization is quite general and useful for substrates with various functional groups.

Exomethylene in 3-methylene-2,3-dihydroindole is a very useful functional group for further transformation. Concerning this exomethylene group, Boger[105] and Sakamoto[106] previously reported hydroboration to introduce a hydroxymethyl group, and Nakagawa[107] and Lectka[108] prepared tryptophan and tryptamine derivatives using an imino-ene reaction. We also found that ozonolysis and RCM can be applied to the synthesis of indoxyl and carbazole derivatives, as shown in Chart 10. Therefore, the cycloisomerization of *N*-allyl-*o*-vinylaniline (**34**) is a new method for the synthesis of 2,3-disubstituted indole derivatives.

Using our methods, substituted 1,2-dihydroquinoline, indole and 3-methylene-2,3-dihydroindole were prepared selectively from the common starting material *N*-allyl-*o*-vinylaniline **34** and catalyst **E** by slight modification of the reaction conditions (Chart 11). These procedures address an important issue in diversity-oriented synthesis.[109]

1.2.3. Actual Active Species of Olefin Isomerization and Cycloisomerization: All of the above methods for heterocycles, including RCM of diene, isomerization of terminal olefin and cycloisomerization of diene, were easily carried out using an argon balloon and the standard Schlenck technique. In the isomerization of alkenes under our reaction conditions, the generation of RuH species should be a key step. Hence, we initially attempted to determine the structure of actual active ruthenium species, for the isomerization of terminal olefin as well as the cycloisomerization of diene, under various conditions using Schlenck technique.[22] However, strong support for our working hypothesis came from the reaction performed in a glovebox, which kept the oxygen and moisture concentrations below 1 ppm. We finally found that the reaction of **E** with **61a** gave ruthenium hydride (**A**) in quantitative yield (Chart 12). Although this catalyst was

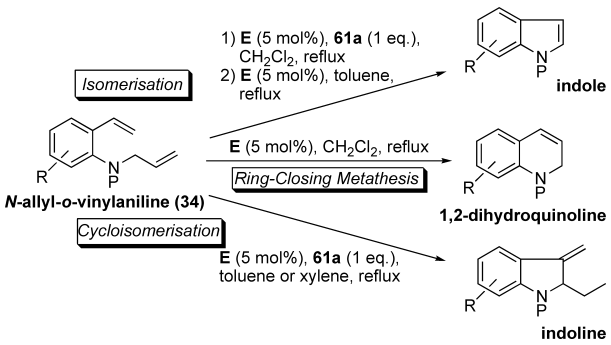


Chart 11. Diversity-Oriented Synthesis of Heterocycles

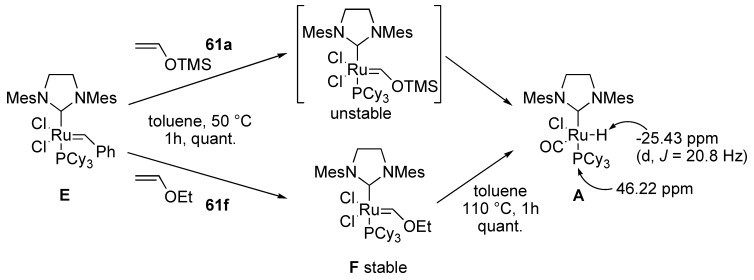


Chart 12. Quantitative Conversion of **E** to **A**

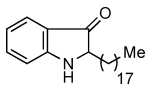


Fig. 6. Reported Structure of Fistulosin

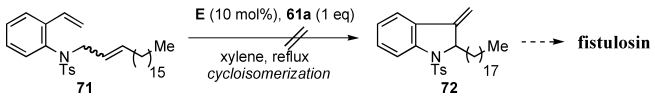
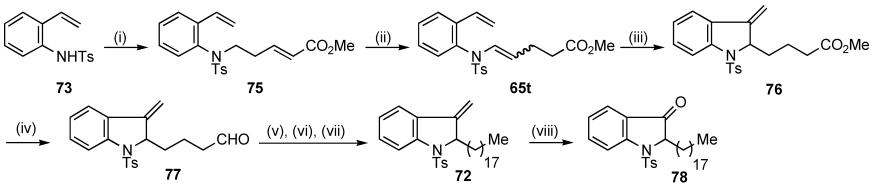


Chart 13. Initial Approach to Fistulosin



Reagents and conditions: (i) (*E*)-HO(CH$_2$)$_2$CH=CHCO$_2$Me (**74**), DEAD, PPh$_3$, THF, rt, 4 h, 99%; (ii) RuClH(CO)(PPh$_3$)$_3$, toluene, reflux, 23 h, 83%; (iii) **E**(10 mol%), **61a** (1 eq.), xylene, reflux, 2 h, 87%; (iv) DIBAL, toluene, -78 °C, 20 min, 87%; (v) BrMg(CH$_2$)$_{13}$Me, THF, 0 °C, 20 min, 93%; (vi) MsCl, Et$_3$N, DMAP, CH$_2$Cl$_2$, rt, 30 min, 86%; (vii) NaBH$_4$, HMPA, 50 °C, 2 h, 71%; (viii) O$_3$, CH$_2$Cl$_2$, -78 °C, 15 min, then PPh$_3$, rt, 2 h, 70%.

Chart 14. Synthesis of *N*-Tosyl-2-octadecyl-3-indolinone (**78**)

easily decomposed under aerobic conditions, it could be stored without any decomposition if kept in a glovebox. Dinger and Mol reported the preparation of **A** from another ruthenium hydride (RuClH(CO)(PCy$_3$)$_2$).[110] Grubbs reported that **A** is generated by the partial decomposition of **E** in MeOH.[111] However, neither method could give **A** with high purity. Our method for converting ruthenium carbene complex to ruthenium hydride complex is general and efficient because of its mildness and the high volatility of side products. In addition, this is the first example to show that **A** can efficiently catalyze the isomerization of terminal olefins and the cycloisomerization of dienes.

When **E** was reacted with **61f** in toluene (0.01 M) at 50 °C for 1 h, Fischer carbene catalyst (**F**) was obtained quantitatively, as reported by Grubbs.[111] Heating of **F** in toluene at 110 °C gave **A** quantitatively. The presence of excess **61f** did not affect the conversion of **F** to **A**. At the same time, **F** has RCM activity[111] but does not have isomerization or cycloisomerization activity. Therefore, in our reaction system (selective isomerization of terminal olefin and cycloisomerization of α,ω-diene), **61f** interferes with **E** from reacting with terminal olefin or α,ω-diene and efficiently converts **E** to **A** through **F**. We found strong evidence for the generation of RuH complex (**A**) in pure form.

1.2.4. Synthesis of the Putative Structure of Fistulosin Using Cycloisomerization as a Key Step[27]: Although the selective and catalytic cycloisomerizations of dienes, in which a new ring is formed without the loss of carbon units, are highly atom-economical reactions, the application of this reaction to the synthesis of natural products or pharmaceutically useful compounds has not been reported because of limitations regarding the range of substrates and the tolerance of functional groups. Hence, we decided to synthesize the reported structure of fistulosin using our cycloisomerization of diene as a key step.

The antifungal indole fistulosin was isolated from the root of Welsh onion (*Allium fistulosum* L.) by Tomita's group in 1999 (Fig. 6).[112] Vegetables in the *Allium* species are known to be rich in flavonoids and alk(en)yl cysteine sulfoxides, which have perceived benefits for human health.[113] Since the late 1980s, biologically active products in *Allium* species have been investigated and the isolation of nematicidal and antibacterial agents has been reported by Tada's group.[114] Furthermore, Tomita's group reported the isolation of the new alkaloid fistulosin, which exhibited antifungal activities against the wilt-producing fungi *Fusarium oxysporum*.[112] In agriculture, antifungal agents isolated from natural products, such as fistulosin, are expected to be useful due to their safety toward animals, humans and ecosystems.

Initially, we planned to synthesize the key intermediate, which has an octadecyl group at the 2-position of the indoline core, from *o*-vinylaniline derivative **71** by ruthenium-catalyzed cycloisomerization. Unfortunately, however, the reaction of **71** in the presence of catalyst **E** and **61a** did not provide the desired cyclized product at all, but rather gave a complex mixture of regioisomers, which were produced by olefin migration of the nonadecenyl side chain (Chart 13).

Therefore, we next chose the enamide **65t** as a substrate for cycloisomerization (Chart 14). This substrate was expected to efficiently undergo our cycloisomerization, and an

ester group was used for subsequent extension of the alkyl chain. The preparation of **65t** began with the Mitsunobu reaction of readily available **73** with alcohol **74**, and treatment of **75** with $RuClH(CO)(PPh_3)_3$[115—118] (10 mol%) provided enamide **65t** in 83% yield. With substrate **65t** in hand, cycloisomerization of **65t** in the presence of Grubbs catalyst **E** (10 mol%) and **61a** (1 eq) in refluxing toluene was carried out and the expected product **76** was obtained as a stable colorless crystal in 87% yield. Installation of a tetradecyl group was achieved through a four-step procedure. Cyclized product **76** was reduced with DIBAL to give aldehyde **77**, and treatment of **77** with Grignard reagent gave the secondary alcohol in 93% yield. Mesylation of the hydroxy group followed by reduction of the mesylate with $NaBH_4$ gave indoline **72**, which was converted to 3-indolinone **78** by ozonolysis. Finally, treatment of **78** with conc. H_2SO_4 at 0 °C[119] gave the deprotected product **79a** quantitatively in crude form (Chart 15). 3-Indolinone **54a** was pure and stable enough to characterize the structure by spectral analyses. However, further purifications of **79a** by column chromatography or recrystallization were unsuccessful, even though we used the same procedure reported by Tomita, since **79a** was gradually tautomerized to more thermodynamically stable 3-hydroxyindole **79b** in solution.[120—122]

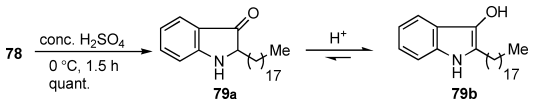
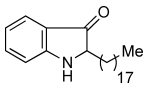
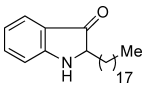
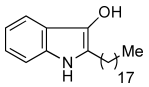
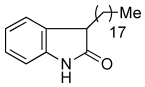


Chart 15. Deprotection and Tautomerization

Next, we compared the spectral data of **79a** to those reported for natural fistulosin (Table 20). The IR spectrum of synthetic compound **79a** revealed a strong band at 1675 cm^{-1}, which was similar to the reported data (1684 cm^{-1}), and the reported characteristic mass peak at 133 [$M-C_{18}H_{36}^+$] was also observed in the spectrum of **79a**. On the other hand, the ^{1}H-NMR spectra showed some remarkable differences. For our synthetic **79a**, the chemical shift of the methine proton at the 2-position was observed at 3.75 ppm, in contrast to 2.44 ppm reported by Tomita's group. In addition, conspicuous differences were seen in the ^{13}C-NMR spectra. For example, the chemical shift of the carbonyl carbon of our sample was observed at 202.7 ppm, in contrast to the reported value of 171.5 ppm. Overall, the spectral data supported the structure of **79a**. Thus, we concluded that the spectral data of **79a** did not agree with those reported for fistulosin.

We next compared the spectral data of the more stable tautomer **79b** and oxindole **80**, which are other candidates for the natural product "fistulosin". Tautomerization of **79a** pro-

Table 20. Comparison of Natural Fistulosin, **79a**, **79b** and **80**

	 Fistulosin (reported)	 **79a** (synthetic)	 **79b** (synthetic)	 **80** (synthetic)
State	White crystal mp 80—83 °C ($CHCl_3$)	Orange solid mp 100—102 °C	Yellow needle mp 107—108 °C (*n*-hexane/AcOEt)	Colorless prism mp 95—96 °C (*n*-hexane)
IR (cm^{-1})	1684 (CO)	1675 (CO)	1674 (OH)	1698 (CO)
MS (EI)	385 (M^+), 133	385 (M^+),161, 133, 84, 18	385 (M^+), 383, 172, 146, 18	385 (M^+), 146, 18
^{1}H-NMR ($CDCl_3$)	10.8 (br s, 1H, NH) 8.8 (d, 1H, *J*=8.37 Hz, CH) 8.1 (d, 1H, *J*=8.12 Hz, CH) 7.6 (t-like, 1H, CH) 7.1 (t-like, 1H, CH) 2.44 (t-like, 1H, CH) 1.74 (m, 2H, CH_2) 1.63 (m, 2H, CH_2) 1.4 (m, 2H, CH_2) 1.25 (br s, 28H, CH_2) 0.88 (t-like, 3H, CH_3)	7.61 (d, 1H, *J*=7.9 Hz) 7.44 (dd, 1H, *J*=8.2, 7.1 Hz) 6.88 (d, 1H, *J*=8.6 Hz) 6.82 (dd, 1H, *J*=7.3, 7.3 Hz) 4.70 (br s, 1H) 3.75 (dd, 1H, *J*=8.4, 4.2 Hz) 1.83—1.96 (m, 1H) 1.55—1.64 (m, 1H) 1.25—1.40 (m, 32H) 0.88 (t, 3H, *J*=6.8 Hz)	7.56 (d, 1H, *J*=7.7 Hz) 7.49 (ddd, 1H, *J*=8.1, 8.1, 0.9 Hz) 6.95 (d, 1H, *J*=8.2 Hz) 6.78 (dd, 1H, *J*=7.1, 7.1 Hz) 6.08 (br s, 1H) 1.84—1.90 (m, 1H) 0.99—1.31 (m, 35H) 0.88 (t, 3H, *J*=6.4 Hz)	8.63 (br s, 1H) 7.22—7.26 (m, 2H) 7.02 (d, 1H, *J*=7.2 Hz) 6.91 (br m, 1H) 3.47 (br m, 1H) 1.96 (br m, 2H) 1.23—1.41 (m, 32H) 0.88 (t, 3H, *J*=6.8 Hz)
^{13}C-NMR ($CDCl_3$)	171.5 (s) 142.5 (s) 135.8 (d) 131.9 (d) 122.7 (d) 120.7 (d) 113.7 (s) 38.9 (s) 32.1 (s) 29.05—29.92 (m) 25.9 (d) 23.4 (s) 14.3 (s)	202.74 161.31 136.94 124.49 121.47 118.85 112.56 64.25 32.04 31.90 29.34—29.68 (m) 25.80 22.67 14.10	204.57 162.00 138.06 124.16 121.54 118.27 111.97 72.51 32.00 31.94 29.33—29.78 (m) 22.95 22.70 14.13	180.73 141.57 129.91 127.72 124.10 122.17 109.66 46.11 31.90 30.53 29.56—29.67 (m) 29.34 25.77 22.67 14.10

ceeded smoothly in an acidic medium, such as aq. HCl or H_2SO_4, to give **79b**, which could be purified by recrystallization from *n*-hexane/AcOEt. Although the crystals of **79b** were not suitable for X-ray analysis, other spectra, including 2D-NMR spectra (^1H–^1H COSY, HMBC and HMQC), unambiguously confirmed the structure of **79b**. Oxindole **80** was synthesized by the procedures reported by Overman and co-workers.[123] However, the spectral data of both **79b** and **80** were also not consistent with those reported for fistulosin (Table 20). Further investigations are necessary to elucidate the structure of fistulosin.

2. Development of Palladium Catalyst Supported on GaAs(001): B

Organopalladium catalysts are very important in organic chemistry and widely used in the synthesis of biologically active compounds.[124,125] The Heck reaction has received considerable attention because it offers a reliable method for carbon–carbon bond formations.[126,127] Like many organic reactions using organometallic reagents and catalysts, the standard procedure under homogeneous conditions suffers from wasted noble metals or catalytically active metals which are difficult to recover and lost in aqueous work-up. With regard to green chemistry, heterogeneous organometallic catalysts are favored and currently being extensively studied.[128—132] However, most of these systems do not give as high a level of activity as homogeneous catalysts. Recently, it has been reported that some heterogeneous catalysts showed a higher activity than homogeneous ones, and the mechanism was studied in detail.[133,134]

We have been aiming at the development of more practical heterogeneous catalysts, which should be active, leach-free and easy to handle, and reported an entirely novel organopalladium catalyst supported on a semiconductor surface, GaAs(001), terminated by a sulfur atom layer using molecular beam epitaxy (MBE)[135] or ammonium sulfide solution (Fig. 7).[136] To the best of our knowledge, no one has reported a semiconductor that is capable of supporting an organometallic catalyst. We expected this new material to amplify the recyclability, or activate differently the aryl halides. In these reports, we have presented the following findings: 1) a {Pd}-S-GaAs(001) plate catalyzed the Heck reaction more efficiently than $Pd(PPh_3)_4$, which is widely used as a homogeneous catalyst, and could be reused at least 10 times, 2) inactivated {Pd}-S-GaAs(001) could be revitalized by further treatment with $Pd(PPh_3)_4$, and 3) sulfur-termination in this catalyst was important for stability of this catalyst.[135,136]

Here, we present a method for preparing {Pd}-S-GaAs(001), which is drastically improved in both catalytic activity and stability. Some chemical and physical properties of the catalyst were elucidated using X-ray photoelectron spectroscopy (XPS), and scanning electron microscopy (SEM). Furthermore, experiments were carried out in order to attempt identification of the real active Pd-species.

As we have previously reported,[136] {Pd}-S-GaAs(001), which is named catalyst **I**, was prepared by a three-step procedure, $(NH_4)_2S_x$ treatment (aqueous solution, 60 °C, 30 min), and Pd adsorption ($Pd(PPh_3)_4$, 7.2 mM, 100 °C, 12 h) followed by washing at room temperature with acetonitrile (MeCN). This catalyst A could be used for the Heck reaction of iodobenzene (**81a**) and methyl acrylate (**82a**) over 10 times (Chart 16). The chemical yield of the 10th run, however, was only 24% and the average chemical yield of 10 runs was 56% (Table 21, entry 1). To identify a more reactive catalyst, we surveyed the sources of Pd. Catalysts **II**—**V** were prepared by the same method as catalyst **I** except for the source of Pd, and then repeatedly subjected to the Heck reaction as shown in Chart 15. The results are summarized in Table 21. Catalyst **II**, prepared with $PdCl_2$, showed almost no activity (entry 2). Catalysts **III** and **IV**, prepared with $Pd(acac)_2$ and $Pd(MeCN)_2Cl_2$, respectively, were unstable and lost most of their catalytic activity before the 7th run (entries 3, 4). Catalyst **V**, prepared with $Pd(dba)_2$, retained its activity until the 10th run, but its activity was lower than that of catalyst **I** (entry 5). In contrast, catalyst **V**, prepared with $Pd(OAc)_2$, had much higher activity than catalyst **I** and the coupling product was obtained in 79% yield in the 10th run (entry 6). Therefore, $Pd(OAc)_2$ is the best source of Pd among those tested for preparing {Pd}-S-GaAs(001).

Next, we examined heated-washing conditions after Pd adsorption, since it is possible that excess Pd on the

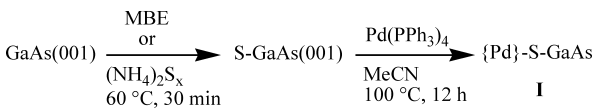


Fig. 7. Preparation of Three-Phase Catalyst, {Pd}-S-GaAs(001), Catalyst **I**

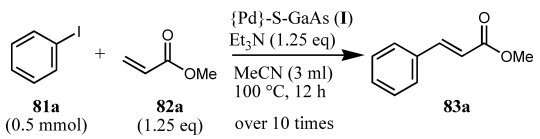


Chart 16. Heck Reaction

Table 21. Effect of Pd Sources in Pd Adsorption

Entry	Cat.	Pd source	Yield of **83a** (%)[a]										
			1st	2nd	3rd	4th	5th	6th	7th	8th	9th	10th	ave.
1	**I**	$Pd(PPh_3)_4$	93	87	71	72	57	54	35	37	25	24	56
2	**II**	$PdCl_2$	1	1	0	—	—	—	—	—	—	—	—
3	**III**	$Pd(acac)_2$	51	31	14	15	10	12	1	—	—	—	—
4	**IV**	$Pd(CH_3CN)_2Cl_2$	43	8	1	0	1	—	—	—	—	—	—
5	**V**	$Pd(dba)_2$	74	66	31	46	12	9	5	1	1	4	25
6	**VI**	$Pd(OAc)_2$	100	99	91	98	97	88	81	72	71	79	88

a) Isolated yields.

Table 22. Effects of Washing Conditions after Pd Adsorption

Entry	Cat.	Pd source	Heated washing	Yield of **83a** (%)[a]										
				1st	2nd	3rd	4th	5th	6th	7th	8th	9th	10th	ave.
1	**I**	$Pd(PPh_3)_4$	No	93	87	71	72	57	54	35	37	25	24	56
2	**VII**	$Pd(PPh_3)_4$	Yes	90	55	67	66	57	54	46	43	43	39	56
3	**VI**	$Pd(OAc)_2$	No	100	99	91	98	97	88	81	72	71	79	88
4	**VIII**	$Pd(OAc)_2$	Yes	96	100	91	93	98	100	96	99	98	95	97

a) The yields were determined by NMR analysis.

Table 23. Optimization of Heated-Washing Conditions

Entry	Cat.	Heated washing		Yield of **83a** (%)[a]										
		Solvent	T (°C)[b]	1st	2nd	3rd	4th	5th	6th	7th	8th	9th	10th	ave.
1	**VIII**	MeCN	100	96	100	91	93	98	100	96	99	98	95	97
2	**IX**	Toluene	100	98	96	92	82	82	63	55	48	62	63	74
3	**X**	DMF	100	98	86	95	89	80	84	75	77	69	70	82
4	**XI**	DMSO	100	88	78	64	38	21	17	16	12	13	14	36
5	**XII**	DMF	135	70	80	78	58	52	49	43	32	31	31	52
6	**XIII**	Toluene	135	95	93	93	97	94	91	91	90	90	85	92
7	**XIV**	Xylene	135	96	100	99	98	100	91	96	97	92	91	96
8	**XV**	Xylene	150	99	99	100	97	99	91	97	94	92	86	95

a) The yields in entry 1 were determined by NMR analysis. The yields in entries 2 to 8 were determined by HPLC analysis. *b*) Bath temperature.

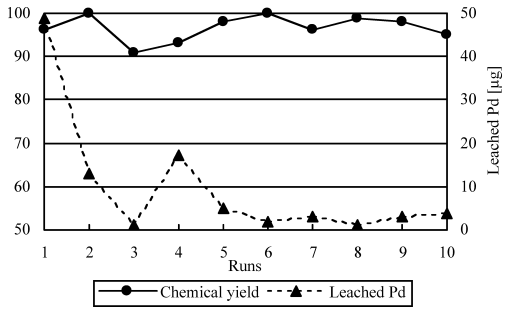


Fig. 8. Chemical Yield and Amount of Leached Pd Using Catalyst **VIII**

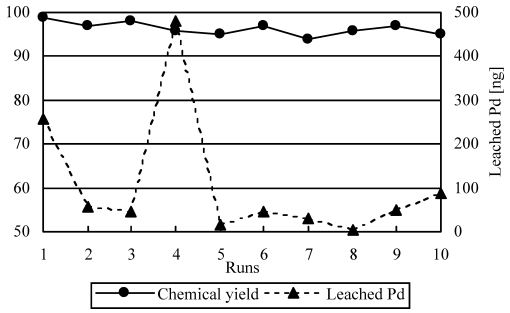


Fig. 9. Chemical Yield and Amount of Leached Pd Using Catalyst **XIV**
Unit of leached Pd is ng not μg.

surface, which is not bound to sulfur, deactivate {Pd}-S-GaAs(001) by forming a less active or inactive colloidal Pd species.[137—139] Hence, catalysts **V** and **VIII** were prepared by a new three-step procedure, which consisted of $(NH_4)_2S_x$ treatment (60 °C, 30 min), Pd adsorption ($Pd(PPh_3)_4$ or $Pd(OAc)_2$, 100 °C, 12 h), and heated-washing in refluxing MeCN. The catalysts were subjected to the same Heck reaction (Chart 15) over 10 times, respectively. As shown in Table 22, the activity of catalyst **VII**, which was prepared with $Pd(PPh_3)_4$ followed by heated-washing, was the same as that of catalyst **I**, which was not treated by heated-washing. In contrast, catalyst **VIII**, which was prepared with $Pd(OAc)_2$, had higher activity than catalyst **VI**, that is, the catalytic activity of **VIII** did not decrease over 10 runs (95%, entry 4), and the average chemical yield over 10 runs was 97%.

We measured the amount of Pd that leached into the reaction solution after the Heck reaction using catalyst **VIII** by inductively coupled plasma mass spectrometry (ICP-Mass). Figure 8 summarizes the chemical yield of the product and the amount of leached Pd in each run. While the chemical yield was almost quantitative through 10 runs, the amount of leached Pd decreased after 4 uses. The amount of Pd leached after the 5th run is a few μg, less than 1.7 ppm. Considering that the amount of immobilized Pd after the 10th run is 125 μg, only trace amounts of Pd were leached after the 5th run.

Unfortunately, after several experiments, we found the reproducibility of the catalytic activity for catalyst **VIII** was poor. Hence, we optimized the heated-washing conditions. First, we carried out the heated-washing using some solvents (Table 23, entries 1—4). Among the solvents we examined, catalyst **VIII**, which had been washed in MeCN at 100 °C (bath temperature), had the best catalytic activity. Next, we continued to examine the effect of solvent in heated-washing at higher temperature (135 °C, bath temperature). We found toluene can be another candidate for heated-washing, but its catalytic activity was lower than that of catalyst **VIII** (entry 6). In entry 7, we carried out heated-washing in xylene at 135 °C. The activity of catalyst **XIV** was as high as that of catalyst **VIII** with good reproducibility and catalyst **XIV** kept its high activity through 10 runs (entry 7). When heated-washing was carried out in xylene at 150 °C, the activity of catalyst **XV** decreased slightly (entry 8).

When catalyst **XIV** was employed, ICP-Mass analysis in-

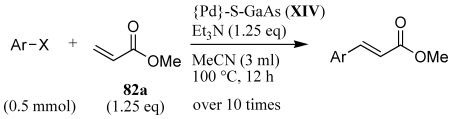
dicated the amount of Pd that leached into the reaction mixture was an extremely low level in each run (0.04—0.26 ppm, Fig. 9). These results suggested that heated-washing in non-coordinated solvent can prepare highly reactive and stable catalysts with good reproducibility and lower leaching, although further experiments are required to explain why these differences in catalytic activities appeared just by changing the solvent and temperature in heated-washing.

Next, to ascertain the scope and limitation of catalyst **XIV**, it was subjected to the Heck reaction of other substrates. The results are summarized in Tables 24 and 25. Bromobenzene (**81b**) and phenyl trifluoromethanesulfonate (**81c**), which are widely used as a substrate for the Heck reaction,[140] were totally inactive under our conditions (Table 24, entries 1, 2). In these cases, catalyst **XIV**, which was used over 5 runs, still possessed catalytic activity for the Heck reaction between **81a** and **82a**, therefore, we assume that our catalyst could not undergo oxidative addition with **81b** and **81c** under these reaction conditions. When 2-, 3-, and 4-iodotoluene were used as substrates, the chemical yields of the corresponding product were varied depending on the position of the methyl group on the aromatic ring (entries 3—5). When 4-iodoanisole (**81g**) was used as a substrate, the reaction proceeded, although the yields decreased gradually (entry 6). When 4-bromo-1-iodobenzene (**81h**) was used, the reaction proceeded chemoselectively to give only 4-bromocinnamate, but the reactivity also gradually decreased (entries 7—9). In entries 10 and 11, the aryl iodides with electron-withdrawing groups at the *para*-position were used to yield the corresponding products at the 1st run, however, after the 2nd run, the chemical yields decreased drastically, and no reactivity was left after the 5th run. In entry 12, 1-iodonaphthalene, which is known for its occasional low activity,[141] was used as a substrate gave the corresponding product in excellent yield over 10 runs and the average yield was 94%. The fact that the non- or de-activated aryl iodides react better than activated ones (entries 3—6 *versus* 8, 9) might suggest that the use of the support modify slightly modified the reaction mechanism, or displaced the limiting step of the reaction from the oxidative addition of the aryl halide to Pd(0) to the reductive elimination to give the expected compound, although we do not have enough data to discuss this matter in detail at this stage.

When methyl vinyl ketone (**82b**) was used instead of **82a**, the chemical yield of the 1st run was 76%,[142—148] and almost the same chemical yield continued through 10 runs.

From these results, we found that our catalyst could catalyze only aryl iodides, and the catalytic activities were also

Table 24. Heck Reaction of Various Aryl Halides

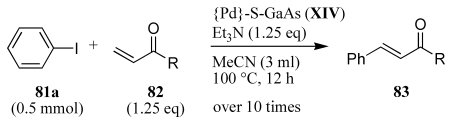


(0.5 mmol) **82a** (1.25 eq) over 10 times

Entry		Substrate [Ar–X] Ar	X		Yield of **83a** (%)[a] 1st	2nd	3rd	4th	5th	6th	7th	8th	9th	10th	ave.
1	**81b**	C_6H_5	Br	**83a**[b]	0	0	0[c]	0[d]	0[e]	—	—	—	—	—	0[f]
2	**81c**	C_6H_5	OTf	**83a**[b]	0	0	0[c]	0[d]	0[e]	—	—	—	—	—	0[f]
3	**81d**	2-MeC_6H_4	I	**83b**	98	90	94	81	72	63	52	49	43	36	68
4	**81e**	3-MeC_6H_4	I	**83c**	100	100	100	72	62	56	59	47	46	38	68
5	**81f**	4-MeC_6H_4	I	**83d**	100	100	100	100	100	100	100	100	98	96	99
6	**81g**	4-$MeOC_6H_4$	I	**83e**	100	92	100	87	75	89	68	48	50	54	76
7	**81h**	2-BrC_6H_4	I	**83f**	92	71	80	57	65	58	36	28	28	25	54
8	**81i**	3-BrC_6H_4	I	**83g**	100	100	81	57	47	39	40	38	25	29	56
9	**81j**	4-BrC_6H_4	I	**83h**	98	81	67	56	65	49	42	41	38	42	58
10	**81k**	4-$NO_2C_6H_4$	I	**83i**	82	34	10	4	0	—	—	—	—	—	26[f]
11	**81l**	4-$MeC(O)C_6H_4$	I	**83j**[g]	91	59	51	44	38	—	—	—	—	—	57[f]
12	**84**	Xylene	I	**85**	99	100	100	99	94	100	83	92	91	83	94

a) Yields were determined by ^{1}H-NMR spectra ($PhNO_2$ (0.25 mmol) was employed as an internal standard.). *b*) Yields were determined by HPLC analysis. *c*) Reaction time was 24 h. *d*) Reaction was carried out in toluene at 135 °C (bath temperature) for 12 h. *e*) Reaction was carried out in toluene at 135 °C (bath temperature) for 24 h. *f*) Average yield through 1 to 5 runs. *g*) 0.50 mmol of acetophenone was used as an internal standard.

Table 25. Heck Reaction of Methyl Vinyl Ketone



81a (0.5 mmol) **82** (1.25 eq) over 10 times **83**

Entry		Substrate (**82**) R		Yield of **83a** (%)[a] 1st	2nd	3rd	4th	5th	6th	7th	8th	9th	10th	ave.
1	**82a**	OMe	**83a**	96	100	99	98	100	91	96	97	92	91	96
2	**82b**	Me	**83k**	76	80	79	78	77	76	72	75	74	71	76

a) Yields were determined by ^{1}H-NMR spectra ($PhNO_2$ (0.25 mmol) was employed as an internal standard.).

influenced by the substituent on aryl iodides.

2.1. Catalysis Properties Based on the above discoveries, we investigated the characteristics of catalyst **VIII** in detail. First, the status of Pd on the surface both before and after these reactions was examined by XPS measurement[149] of catalyst **VIII** using Mg ka radiation (K.E.＝1253 eV) in a separate ultra-high-vacuum chamber. The energy shift due to sample charging was corrected as the C 1s peak is located at 285.0 eV. The XPS spectrum of catalyst H before the Heck reaction exhibited clear peaks of Pd 3d core-level photoemission, indicating that the organopalladium was definitely immobilized as expected (spectrum I in Fig. 10). The peak width is slightly wider than that of metal Pd (not shown), suggesting a complex chemical environment and/or partial oxidation of Pd. The binding energy of the Pd 3d5/2 peak, 335.9 eV, is close to that of metal Pd, 335.0 eV, indicating that the valence of Pd is zero,[150] while that of the Pd source, $Pd(OAc)_2$, is 2. Even after repeated cycles of the Heck reaction, catalyst **VIII** showed almost the same Pd 3d peaks (spectrum II in Fig. 10), suggesting that the oxidation state of the immobilized Pd did not change in the repeated Heck reactions.

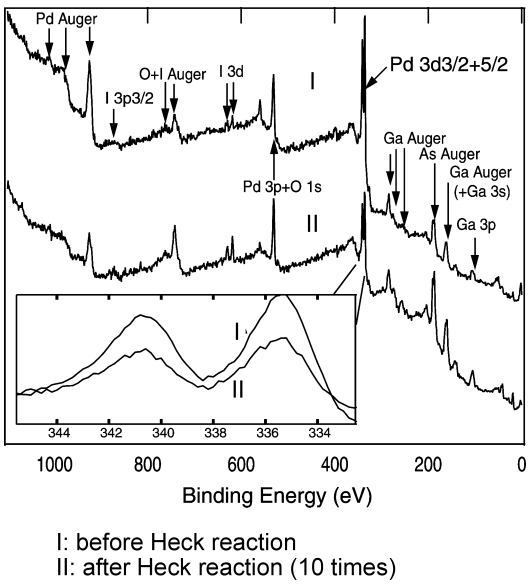
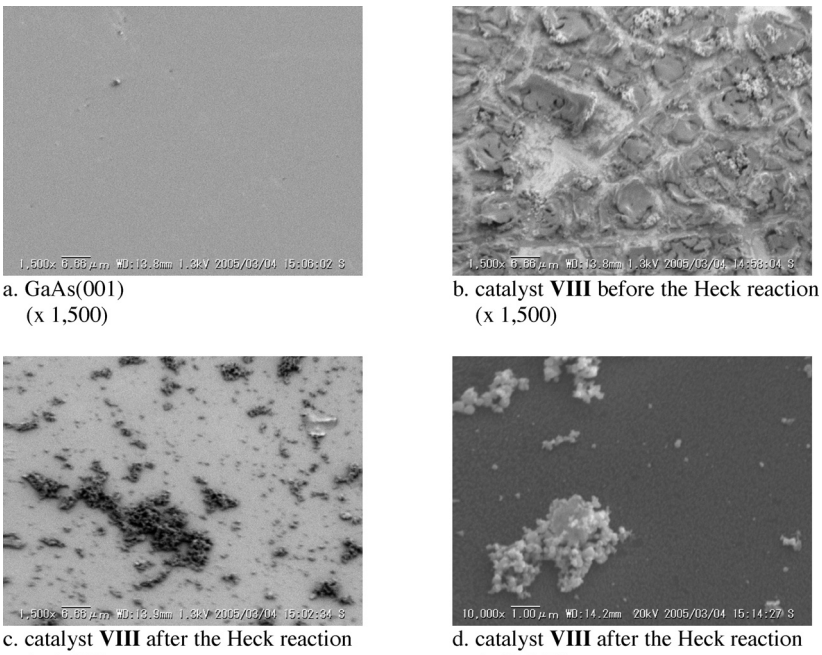


Fig. 10. XPS Spectra of Catalyst **VIII**

Second, to obtain further information about the surface both before and after 10 runs of the Heck reaction, catalyst **VIII** was directly surveyed by SEM and compared to the GaAs(001) substrate. As shown in Fig. 11, catalyst **VIII** before the Heck reaction had a characteristic structure on GaAs(001) (b) and after 10 runs of the Heck reaction, the surface structure was obviously changed (c and d), although the catalytic activity showed no significant difference between the 1st run and the 10th run of the Heck reaction.

2.2. Mechanistic Study Identification of the real catalyst is one of the important problems in the development of a novel heterogeneous catalyst.[133,134] First, we conducted a three-phase test.[151,152] This test can clarify which soluble or insoluble species is the real active catalyst by running a metal-catalyzed reaction in the presence of a substrate immobilized on polymer. We prepared the immobilized iodobenzene (**87**) according to Davies' protocol,[153] and carried out the Heck reaction of **81a** and **87** with **82a** in the presence of {Pd}-S-GaAs, catalyst **XIV** (Chart 17). After the reaction mixture was refluxed for 12 h, the catalyst was removed. Then the reaction mixture was filtered. From the filtrate, 2% of coupling product **83a** was obtained. The resin was treated with an excess amount of trifluoroacetic acid (TFA) at room temperature for 2 h to give **88** in 30% yield. As a control, we ran the Heck reaction of only **87** using {Pd}-S-GaAs. In this case, the coupling product **88** was not obtained. Furthermore, using a homogeneous catalyst, $Pd(OAc)_2$, the Heck reaction proceeded to give **88** in 62% yield.



a. GaAs(001) (x 1,500)

b. catalyst **VIII** before the Heck reaction (x 1,500)

c. catalyst **VIII** after the Heck reaction (x 1,500)

d. catalyst **VIII** after the Heck reaction (x 10,000)

Fig. 11. SEM Observation of Catalyst **VIII**

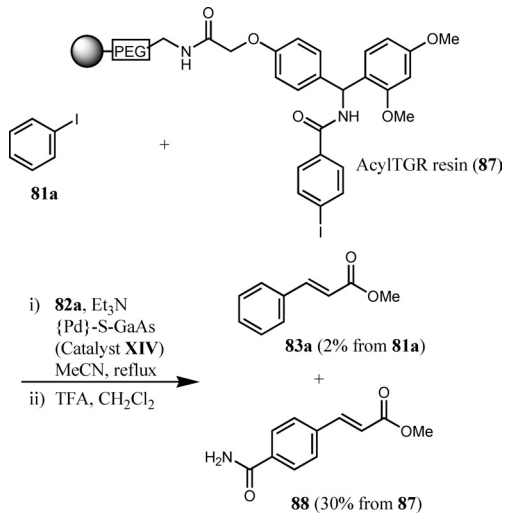


Chart 17. Three Phase Test

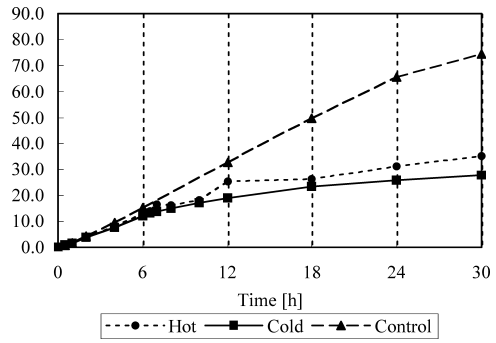


Fig. 12. Hot and Cold Filtration Tests

Next, we examined hot and cold filtration tests to see whether leached Pd species have catalytic activity for the Heck reaction.[154] A mixture of **81a**, **82a**, Et_3N, and {Pd}-S-GaAs in MeCN was refluxed for 6 h without stirring, and then the catalyst was removed from the 'hot' mixture. The yield of **83a** was 13% in this step. The 'hot' solution was continuously refluxed without {Pd}-S-GaAs. After 24 h (total time 30 h), the yield of **83a** was 35%. In addition, a mixture of **81a**, **82a**, Et_3N, and {Pd}-S-GaAs in MeCN was refluxed for 6 h without stirring. After the mixture was cooled to room temperature, the catalyst was removed from the 'cold' mixture. The yield of **83a** was 13% in this step. The 'cold' clear solution was refluxed for 24 h (total time 30 h) without {Pd}-S-GaAs to give **83a** in 28% yield. In both cases, the product increased, even if the catalyst was removed from the reaction mixture. However, these chemical yields were much lower than that of the reaction in which {Pd}-S-GaAs was employed from the beginning to the end.

Considering that there is no relationship between chemical yield and amount of leached Pd (Figs. 2, 3) for the Heck reaction, these results indicate: 1) During the Heck reaction, a trace amount of Pd species was leached from {Pd}-S-GaAs into the reaction mixture. 2) The leached Pd species has some activity in the Heck reaction. 3) The catalytic activity of leached Pd is lower than that of {Pd}-S-GaAs. 4) For a highly efficient Heck reaction, the presence of {Pd}-S-GaAs is critical, although we do not know if {Pd}-S-GaAs works as the actual active species or the pre-catalyst.

We have successfully developed a method for preparing {Pd}-S-GaAs(001) (**B**), the catalytic activity of which for the Heck reaction does not decrease after 10 uses and which shows only trace amounts of Pd leached into the reaction mixture after the 5th run. In addition, it was clear that the immobilized Pd on S-GaAs(001) is Pd(0). This catalyst is easy to recover and transfer under air using a pair of tweezers. We hope that this catalyst might lead to new opportunities in environmentally benign immobilized catalysts and microreactors.

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References

1) For recent reviews of olefin metathesis, see: Connon S. J., Blechert S., *Angew. Chem. Int. Ed.*, **42** 1900—1923 (2003).
2) Deiters A., Martin S. F., *Chem. Rev.*, **104**, 2199—2238 (2004).
3) Grubbs R. H., *Tetrahedron*, **60**, 7117—7140 (2004).
4) Armstrong S. K., *Chem. Soc., Perkin Trans. 1*, **1998**, 371—388 (1998).
5) Schwab P., Grubbs R. H., Ziller J. W., *J. Am. Chem. Soc.*, **118**, 100—110 (1996).
6) Schwab P., France M. B., Ziller J. W., Grubbs R. H., *Angew. Chem. Int. Ed.*, **34**, 2039—2041 (1995).
7) Scholl M., Trnka T. M., Morgan J. P., Grubbs R. H., *Tetrahedron Lett.*, **40**, 2247—2250 (1999).
8) Scholl M., Ding S., Lee C. W., Grubbs R. H., *Org. Lett.*, **1**, 953—956 (1999).
9) Chatterjee A. K., Grubbs R. H., *Org. Lett.*, **1**, 1751—1753 (1999).
10) Kingsbury J. S., Harrity J. P. A., Bonitatebus, P. J., Jr., Hoveyda A. H., *J. Am. Chem. Soc.*, **121**, 791—799 (1999).
11) Arisawa M., Takezawa E., Nishida A., Mori M., Nakagawa M., *Synlett*, **1997**, 1179—1180 (1997).
12) Nakagawa M., Uchida H., Torisawa Y., Nishida A., *J. Synth. Org. Chem. Jpn.*, **57**, 1004—1005 (1999).
13) Arisawa M., Kato C., Kaneko H., Nishida A., Nakagawa M., *J. Chem. Soc. Perkin Trans. I*, **2000**, 1873—1876 (2000).
14) Arisawa M., Kaneko H., Nishida A., Yamaguchi K., Nakagawa M., *Synlett*, **2000**, 841—843 (2000).
15) Arisawa M., Takahashi M., Takezawa E., Yamaguchi T., Torisawa Y., Nishida A., Nakagawa M., *Chem. Pharm. Bull.*, **48**, 1593—1596 (2000).
16) Arisawa M., Theeraladanon C., Nishida A., Nakagawa M., *Tetrahedron Lett.*, **42**, 8029—8033 (2001).
17) Arisawa M., Kaneko H., Nishida A., Nakagawa M., *J. Chem. Soc. Perkin Trans. I*, **2002**, 959—964 (2002).
18) Arisawa M., Terada Y., Nakagawa M., Nishida A., *Angew. Chem. Int.*

Ed., **41**, 4732—4734 (2002).
19) Nagata T., Nakagawa M., Nishida A., *J. Am. Chem. Soc.*, **125**, 7484—7485 (2003).
20) Ono K., Nakagawa M., Nishida A., *Angew. Chem. Int. Ed.*, **43**, 2020—2023 (2004).
21) Theeraladanon C., Arisawa M., Nishida A., Nakagawa M., *Tetrahedron*, **60**, 3017—3035 (2004).
22) Terada Y., Arisawa M., Nakagawa M., Nishida A., *Angew. Chem. Int. Ed.*, **43**, 4063—4067 (2004).
23) Terada Y., Arisawa M., Nishida A., *Chemical Times*, **194**, 2—10 (2004).
24) Theeraladanon C., Arisawa M., Nakagawa M., Nishida A., *Tetrahedron: Asymmetry*, **16**, 827—831 (2005).
25) Arisawa M., Terada Y., Theeraladanon C., Takahashi K., Nakagawa M., Nishida A., *J. Organomet. Chem.*, **690**, 5398—5406 (2005).
26) Arisawa M., Theeraladanon C., Nishida A., *Heterocycles*, **66**, 683—688 (2005).
27) Terada Y., Arisawa M., Nishida A., *J. Org. Chem.*, **71**, 1269—1272 (2006).
28) Arisawa M., Terada Y., Takahashi K., Nakagawa M., Nishida A., *J. Org. Chem.*, **71**, 4255—4261 (2006).
29) Arisawa M., Nishida A., Nakagawa M., *J. Organomet. Chem.*, **691**, 5109—5121 (2006).
30) Arisawa M., Terada Y., Takahashi K., Nakagawa M., Nishida A., *The Chem. Record*, **7**, in press (2007).
31) Giannis A., Kolter T., *Angew. Chem. Int. Ed. Engl.*, **32**, 1244—1267 (1993).
32) Michael J. P., *Nat. Prod. Rep.*, **16**, 675—696 (1999).
33) Michael J. P., *Nat. Prod. Rep.*, **15**, 571—594 (1998).
34) Liddell J. R., *Nat. Prod. Rep.*, **15**, 363—370 (1998).
35) Paolucci C., Musiani L., Venturelli F., Fava A., *Synthesis*, **1997**, 1415—1419 (1997).
36) Uchida H., Nishida A., Nakagawa M., *Tetrahedron Lett.*, **40**, 113—116 (1999).
37) Torisawa Y., Than S., Katoh C., Motohashi Y., Nishida A., Hino T., Nakagawa M., *Heterocycles*, **42**, 655—659 (1998).
38) Torisawa Y., Hosaka T., Tanabe K., Suzuki N., Motohashi Y., Hino T., Nakagawa M., *Tetrahedron*, **52**, 10597—10608 (1996).
39) Nakagawa M., Torisawa Y., Hosaka T., Tanabe K., Date T., Okamura K., Hino T., *Tetrahedron Lett.*, **34**, 4543—4546 (1993).
40) Torisawa Y., Nakagawa M., Hosaka T., Tanabe K., Lai Z., Ogata K., Nakata T., Ohishi T., Hino T., *J. Org. Chem.*, **57**, 5741—5747 (1992).
41) Tarling D. A., Holmes A. B., Markwell R. E., Pearson N. D., *J. Chem. Soc., Perkin Trans. 1*, **1999**, 1695—1701 (1999).
42) Diedrichs N., Wetermann B., *Synlett*, **1999**, 1127—1129 (1999).
43) Martin S. F., Humphrey J. M., Ali A., Hillier M. C., *J. Am. Chem. Soc.*, **121**, 866—867 (1999).
44) Pandit U. K., Overekleeft H. S., Borer B. C., Bieräugel H., *Eur. J. Org. Chem.*, **1999**, 959—968 (1999).
45) Grossmith C. E., Senia F., Wagner J., *Synlett*, **1999**, 1660—1662 (1999).
46) Sakai R., Kohmoto S., Higa T., Jefford C. W., Bernardinelli G., *Tetrahedron Lett.*, **28**, 5493—5496 (1987).
47) Torisawa Y., Hashimoto A., Nakagawa M., Hino T., *Tetrahedron Lett.*, **30**, 6549—6550 (1989).
48) Torisawa Y., Hashimoto A., Nakagawa M., Seki H., Hara R., Hino T., *Tetrahedron*, **47**, 8067—8078 (1991).
49) Nowak W., Gerlach H., *Liebigs Ann. Chem.*, **1993**, 153—159 (1993).
50) Vidal T., Magnier E., Langlois Y., *Tetrahedron*, **54**, 5959—5966 (1998).
51) Torisawa Y., Hashimoto A., Okouchi M., Iimori T., Nagasawa M., Hino T., Nakagawa M., *Bioorg. Med. Chem. Lett.*, **6**, 2565—2570 (1996).
52) Sukkari H. E., Gesson J.-P., Renoux B., *Tetrahedron Lett.*, **39**, 4043—4046 (1998).
53) Nishida A., Yamanaka M., Nakagawa M., *Tetrahedron Lett.*, **40**, 1555—1558 (1999).
54) Alkene metathesis; macrolactams: Fürstner A., Dierkes T., Thiel O. R., Blanda G., *Chem. Eur. J.*, **7**, 5286—5298 (2001).
55) Fürstner A., Thiel O. R., Ackermann L., *Org. Lett.*, **3**, 449—451 (2001).
56) Fürstner A., Thiel O. R., Kindler N., Bartkowska B., *J. Org. Chem.*, **65**, 7990—7995 (2000).
57) Lee C. W., Grubbs R. H., *Org. Lett.*, **2**, 2145—2147 (2000).
58) Fürstner A., Thiel O. R., Blanda G., *Org. Lett.*, **2**, 3731—3734 (2000).
59) Goldring W. P. D., Hodder A. S., Weiler L., *Tetrahedron Lett.*, **39**, 4955—4958 (1998).
60) Fürstner A., Langemann K., *Synthesis*, **1997**, 792—803 (1997).
61) Fürstner A., Langemann K., *J. Org. Chem.*, **61**, 3942—3943 (1996).
62) Alkyne metathesis; Fürstner A., Mathes C., Lehmann C. W., *Chem. Eur. J.*, **7**, 5299—5317 (2001).
63) Fürstner A., Guth O., Rumbo A., Seidel G., *J. Am. Chem. Soc.*, **121**, 11108—11113 (1999).
64) Fürstner A., Seidel G., *Angew. Chem. Int. Ed.*, **37**, 1734—1736 (1998).
65) Jin S. J., Tserng K. Y., *Biochemistry*, **29**, 8540—8547 (1990).
66) For examples, ruthenium-catalyzed versions; Tsuji Y., Huh K. T., Watanabe Y., *J. Org. Chem.*, **52**, 1673—1680 (1987).
67) Cho C. S., Oh B. H., Kim J. S., Kim T.-J., Shim S. C., *Chem. Commun.*, **2000**, 1885—1886 (2000).
68) Evans P. A., Robinson J. E., Moffett K. K., *Org. Lett.*, **3**, 3269—3271 (2001).
69) Palladium-catalyzed versions; Cortese N. A., Ziegler C. B., Hrnjez B. J., Heck R. F., *J. Org. Chem.*, **43**, 2952—2958 (1978).
70) Hegedus L. S., Allen G. F., Bozell J. J., Waterman E. L., *J. Am. Chem. Soc.*, **100**, 5800—5807 (1978).
71) Laborde E., Lesheski L. E., Kiely J. S., *Tetrahedron Lett.*, **31**, 1837—1840 (1990).
72) Larock R. C., Kuo M. Y., *Tetrahedron Lett.*, **32**, 569—572 (1971).
73) Kundu N. G., Mahanty J. S., Das P., Das B., *Tetrahedron Lett.*, **34**, 1625—1628 (1993).
74) Dupont J., Halfen R. A. P., Zinn F. K., Pfeffer M., *J. Organomet. Chem.*, **484**, c8—c9 (1994).
75) Cacchi S., Fabrizi G., Marinelli F., *Synlett*, **1999**, 401—404 (1999).
76) Pita B., Masaguer C. F., Ravina E., *Tetrahedron Lett.*, **43**, 7929—7932 (2002).
77) Hatano M., Mikami K., *J. Am. Chem. Soc.*, **125**, 4704—4705 (2003).
78) Rhodium-catalyzed versions; Diamond S. E., Szalkiewicz A., Mares F., *J. Am. Chem. Soc.*, **101**, 490—491 (1979).
79) Watanabe Y., Yamamoto M., Shim S. C., Mitsudo T., Takegami Y., *Chem. Lett.*, **1979**, 1025—1026 (1979).
80) Watanabe Y., Suzuki N., Shim S. C., Yamamoto M., Mitsudo T., Takegami Y., *Chem. Lett.*, **1980**, 429—430 (1980).
81) Boyle W. J., Mares F., *Organometallics*, **1**, 1003—1006 (1982).
82) Amii H., Kishikawa Y., Uneyama K., *Org. Lett.*, **3**, 1109—1112 (2001).
83) Iron-catalyzed version; Watanabe Y., Takatsuki K., Shim S. C., Mitsudo T., Takegami Y., *Bull. Chem. Soc. Jpn.*, **51**, 3397—3398 (1978).
84) Copper-catalyzed version; Huma H. Z. S., Halder R., Kalra S. S., Das J., Iqbal J., *Tetrahedron Lett.*, **43**, 6485—6488 (2002).
85) Manganese-catalyzed version; Kobayashi K., Nakahashi R., Mano M., Morikawa O., Konishi H., *Bull. Chem. Soc. Jpn.*, **76**, 1257—1259 (2003).
86) Cobalt-catalyzed version; Domínguez G., Casarrubios L., Rodríguez-Noriega J., Pérez-Castells J., *Helv. Chim. Acta*, **85**, 2856—2861 (2002).
87) Nishida A., Sorimachi H., Iwaida M., Matsumizu M., Kawate T., Nakagawa M., *Synlett*, **1998**, 389—390 (1998).
88) Turner R. B., Woodward R. B., "The Alkaloids," Vol. 3, Chap. 16, ed. by Manske R. H. F., Academic Press, New York, 1953, pp. 1—63.
89) Uskokoviac M. R., Grethe G., "The Alkaloids," Vol. 14, ed. by Manske R. H. F., Academic Press, New York, 1973, pp. 181—223.
90) Grethe G., Uskokovic M. R., "The Chemistry of Heterocyclic Compounds," Vol. 23, Part 4, ed. by Sexton J. E., Wiley-Interscience, New York, 1983, p. 279.
91) Dutta N. L., Quassim C., *Indian J. Chem.*, **6**, 566—567 (1968).
92) For stereoselective total synthesis: Stork G., Niu D., Fujimoto A., Koft E. R., Balkovec J. M., Tata J. R., Dake G. R., *J. Am. Chem. Soc.*, **123**, 3239—3242 (2001).
93) Andersag H., Breitner S., Jung H., German Patent 683692 (1939) [*Chem. Abstr.*, **36**, 4973 (1942)].
94) Andersag H., Breitner S., Jung H., US Patent 2233970 (1941) [*Chem. Abstr.*, **35**, 3771 (1941)].
95) Jacquemond-Collet I., Hannedouche S., Fabre N., Fourste I., *Phytochemistry*, **51**, 1167—1169 (1999).
96) Rakotoson J. H., Fabre N., Jacquemond-Collet I., Hannedouche S.,

Fourste I., Moulis C., *Planta Med.*, **64**, 762—763 (1998).
97) Mester I., *Fitoterapia*, **44**, 123—152 (1973).
98) Houghton P. J., Woldemariam T. Z., Watanabe T., Yates M., *Planta Med.*, **65**, 250—254 (1999).
99) Jacquemond-Collet I., Benoit-Vical F., Mustofa, Valentin A., Stanislas E., Mallie M., *Planta Med.*, **68**, 68—69 (2002).
100) Wang W., Lu S., Yang P., Han X., Zhou Y., *J. Am. Chem. Soc.*, **125**, 10536—10537 (2003).
101) Mitsunobu O., *Synthesis*, **1981**, 1—28 (1981).
102) Kadnikov D. V., Larock R. C., *J. Org. Chem.*, **69**, 6772—6780 (2004).
103) Nagata T., Koide Y., Nara K., Itoh E., Arisawa M., Naruto S., Torisawa Y., Hino T., Nakagawa M., *Chem. Pharm. Bull.*, **44**, 451—453 (1996).
104) Nakamura I., Yamamoto Y., *Chem. Rev.*, **104**, 2127—2198 (2004).
105) Boger D. L., Ishizaki T., Wysocki R. J., Jr., Munk S. A., *J. Am. Chem. Soc.*, **111**, 6461—6463 (1989).
106) Sakamoto T., Kondo Y., Uchiyama M., Yamanaka H., *J. Chem. Soc., Perkin Trans. 1*, **1993**, 1941—1942 (1993).
107) Yamanaka M., Nishida A., Nakagawa M., *J. Org. Chem.*, **68**, 3112—3120 (2003).
108) Ferraris D., Young B., Cox C., Dudding T., Drury W. J., III, Ryzhkov L., Taggi A. E., Lectka T., *J. Am. Chem. Soc.*, **124**, 67—77 (2002).
109) Burke M. D., Schreiber S. L., *Angew. Chem. Int. Ed.*, **43**, 46—58 (2004).
110) Dinger M. B., Mol J. C., *Eur. J. Inorg. Chem.*, **2003**, 2827—2833 (2003).
111) Louie J., Grubbs R. H., *Organometallics*, **21**, 2153—2164 (2002).
112) Phay N., Higashiyama T., Tsuji M., Matsuura H., Fukushi Y., Yokota A., Tomita F., *Phytochemistry*, **52**, 271—274 (1999).
113) For a review of biologically active compounds in onions, see: Griffiths G., Trueman L., Crowther T., Thomas B., Smith B., *Phytother. Res.*, **16**, 603—615 (2002).
114) Tada M., Hiroe Y., Kiyohara S., Suzuki S., *Agric. Biol. Chem.*, **52**, 2383—2385 (1988).
115) Wakamatsu H., Nishida M., Adachi N., Mori M., *J. Org. Chem.*, **65**, 3966—3970 (2000).
116) van Otterlo W. A. L., Ngidi E. L., de Koning C. B., *Tetrahedron Lett.*, **44**, 6483—6486 (2003).
117) van Otterlo W. A. L., Pathak R., de Koning C. B., *Synlett*, **2003**, 1859—1861 (2003).
118) van Otterlo W. A. L., Morgans G. L., Khanye S. D., Aderibigbe B. A. A., Michael J. P., Billing D. G., *Tetrahedron Lett.*, **45**, 9171—9175 (2004).
119) Hirokawa Y., Harada H., Yoshikawa T., Yoshida N., Kato S., *Chem. Pharm. Bull.*, **50**, 941—959 (2002).
120) For 3-hydroxyindoles, see: Capon B., Kwok F.-C., *J. Am. Chem. Soc.*, **111**, 5346—5356 (1989).
121) Hickman Z. L., Sturino C. F., Lachance N., *Tetrahedron Lett.*, **41**, 8217—8220 (2000).
122) Kirby G. W., Shah S. W., *Chem. Commun.*, **1965**, 381a (1965).
123) Huang A., Kodanko J. J., Overman L. E., *J. Am. Chem. Soc.*, **126**, 14043—14053 (2004).
124) Negishi E., "Handbook of Organopalladium Chemistry for Organic Synthesis," Wiley Interscience, New York, 2002.
125) Tsuji J., "Palladium Reagents and Catalysts," Wiley, Chichester, 2004.
126) Beletskaya I. P., Cheprakov A. V., *Chem. Rev.*, **100**, 3009—3066 (2000).
127) Biggis A., Zecca M., Basato M., *J. Mol. Catal. A*, **173**, 249—274 (2001).
128) Fan Q.-H., Li Y.-M., Chan A. S. C., *Chem. Rev.*, **102**, 3385—3466 (2002).
129) Leadbeater N. E., Marco M., *Chem. Rev.*, **102**, 3217—3274 (2002).
130) Song C. E., Lee S.-G., *Chem. Rev.*, **102**, 3495—3524 (2002).
131) Dupont J., de Souza R. F., Auarez P. A. Z., *Chem. Rev.*, **102**, 3667—3692 (2002).
132) Kobayashi J., Mori Y., Okamoto K., Akiyama R., Ueno M., Kitamori T., Kobayashi S., *Science*, **304**, 1305—1308 (2005).
133) Ji Y., Jain S., Davis R. J., *J. Phys. Chem. B*, **109**, 17232—17238 (2005).
134) Zhao F., Shirai M., Lkushima Y., Arai M., *J. Mol. Catal. A: Chem.*, **180**, 211—219 (2002).
135) Arisawa M., Tsukamoto S., Shimoda M., Pristovsek M., Nishida A., *Jpn. J. Appl. Phys.*, **41**, L1197—L1199 (2002).
136) Takamiya I., Tsukamoto S., Shimoda M., Miyashita N., Arisawa M., Arakawa Y., Nishida A., *Chem. Lett.*, **33**, 1208—1209 (2004).
137) Herrmann W. A., Brossmer C., Öfele K., Beller M., Fisher H., *J. Mol. Catal. A: Chem.*, **103**, 133—146 (1995).
138) Beller M., Fisher H., Kühlein K., Reisinger C. P., Herrman W. A., *J. Organomet. Chem.*, **520**, 257—259 (1996).
139) Djakovitch L., Koehler K., *J. Am. Chem. Soc.*, **123**, 5990—5999 (2001).
140) Gruber M., Chouzier S., Koehler K., Djakovitch L., *Appl. Catal. A: General*, **265**, 161—169 (2004).
141) Xiong Z., Wang N., Dai M., Li A., Chen J., Yang Z., *Org. Lett.*, **6**, 3337—3340 (2004).
142) Reactivity of methyl vinyl ketone is usually lower than that of methyl acrylate. 76% of chemical yield is useful in literatures: Botella L., Nájera C., *J. Org. Chem.*, **70**, 4360—4369 (2005).
143) Botella L., Nájera C., *Tetrahedron Lett.*, **45**, 1833—1836 (2004).
144) Yang D., Chen Y.-C., Zhu N.-Y., *Org. Lett.*, **6**, 1577—1580 (2004).
145) Cacchi S., Fabrizi G., Goggiamani A., *Arkivoc*, **2003**, 58—66 (2003).
146) Hagiwara H., Shimizu Y., Hoshi T., Suzuki T., Ando M., Ohkubo K., Yokoyama C., *Tetrahedron Lett.*, **42**, 4349—4351 (2001).
147) Clark J. H., Macquarrie D. J., Mubofu E. B., *Green Chem.*, **2**, 53—56 (2000).
148) Cacchi S., Fabrizi G., Gasparrini F., Villani C., *Synlett*, **1999**, 345—347 (1999).
149) Shimoda M., Tsukamoto S., Koguchi N., *Surf. Sci.*, **402**, 669—672 (1998).
150) The palladium(II) 3d5/2 peak from $PdCl_2$ is observed at 338.3 eV.
151) Rebek J., Gavina F., *J. Am. Chem. Soc.*, **96**, 7112—7114 (1974).
152) Rebek J., Brown D., Zimmerman S., *J. Am. Chem. Soc.*, **97**, 454—455 (1975).
153) Davies I. A., Matty L., Hughes D. L., Reider P. J., *J. Am. Chem. Soc.*, **123**, 10139—10140 (2001).
154) Baleizao C., Corma A., Garcia H., Leyva A., *J. Org. Chem.*, **69**, 439—446 (2004).