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Preparation of nitrogen-containing heterocycles using ring-closing metathesis (RCM) and its application to natural product synthesis

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Abstract

Our synthetic study of nitrogen-containing heterocycles using ring-closing metathesis (RCM), such as chiral bicyclic lactams, azacycloundecenes, axially chiral macrolactams, 1,2-dihydroquinolines, 2-quinolinones and indoles, including a development of silyl-enol ether ene metathesis and isomerization of terminal olefins, are described. Their applications to natural product synthesis are also reported.

Keywords: Nitrogen-containing heterocycles; Ring-closing metathesis (RCM); Chiral bicyclic lactams; Azacycloundecenes; Axially chiral macrolactams; 1,2-dihydroquinolines; 2-quinolinones; Indoles; Silyl-enol ether ene metathesis; Isomerization of terminal olefins; Natural product synthesis

1. Introduction

Transition metal-catalyzed olefin metathesis is a remarkable 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]. Over the past decades, well-defined ruthenium catalysts have been developed since Grubbs and coworkers reported the first practical catalyst (**B**) [2]. The recent introduction of catalysts (**C** [3], **E** [4]) bearing *N*-heterocyclic carbene (NHC) ligand has led to much higher reactivity (Fig. 1). More than 10 years, we have been exploring a synthetic methodology for nitrogen-containing heterocycles using these ruthenium–carbene catalysts which then applied to the synthesis of biologically active natural products [5].

In this account, we describe our synthetic study of nitrogen-containing heterocycles using 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 natural products synthesis, (−)-coniceine, (*S*)-pyrrolam A and angustureine.

2. Chiral bicyclic lactams, synthesis of (−)-coniceine and (*S*)-pyrrolam A [5a,5e]

Biologically active alkaloids having an azabicyclic framework are abundant in nature. The pyrroloazocine, pyrroloazepine, quinolizidine, indolizidine alkaloids fall into this category and have attracted considerable attention from both the synthetic viewpoint and their biological activities [6,7]. As a part of our program [8] 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 has been investigated. We first studied RCM of chiral dienes which were readily prepared from L-proline (Table 1).

The overall procedure consisted of the RCM reaction of chiral dienes (**1**–**5**) in the presence of catalyst (**A** and **B**) to

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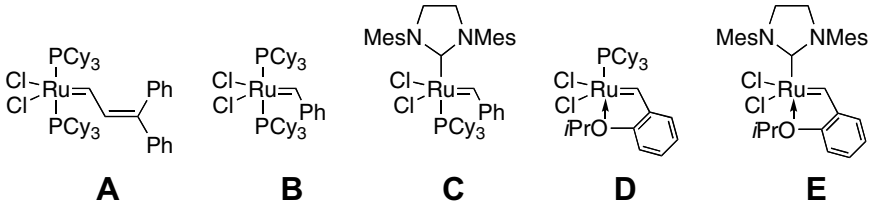


Fig. 1. Ruthenium catalysts.

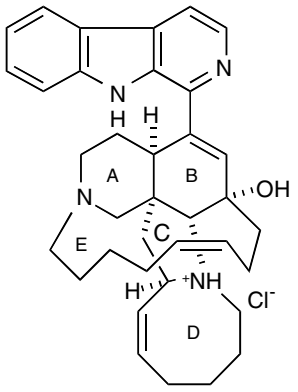


Fig. 2. Structure of manzamine **A**.

form the corresponding bicyclic lactam (**6**–**9**). RCM reaction of these dienes is quite interesting, since expected azabicyclic compounds offer tremendous utility as reaction intermediates in organic synthesis. When **1** was treated with 5 mol% of catalyst **A** in degassed benzene (20 mM) at rt for 3 days, indolizidine **6** was obtained in 93% yield (Entry 1). The reaction of **1**, on the other hand, proceeded more rapidly with catalyst **B**, giving **6** in 66% yield within 18 h (Entry 2). Similar cyclization of **2** with catalyst B gave **7** also proceeded more rapidly with catalyst **B** and **7** was obtained in 73% yield (Entry 3).

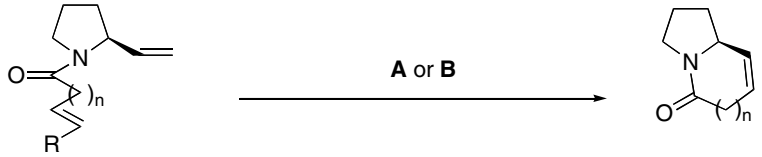
In contrast to the cyclization to six- and seven-membered rings, initial attempted reaction of a diene **3** to five-membered lactam **8** under similar conditions (20 mM, r.t.) using 10 mol% of **A** in benzene was unsuccessful, probably due to the formation of stable chelated species. Therefore, we studied RCM of **4** at elevated temperature (50 °C) and the expected cyclization to **8** took place to give (*S*)-pyrrolam A (**8**) in 30% yield (Entry 4). The low yield observed in the formation of **8** was probably due to the instability of the product under reaction conditions.

Next we studied construction of a medium ring such as **9**, which corresponds to the CD ring in manzamine A. Although in many cases intramolecular cyclization to eight-membered ring systems did not proceed efficiently, several groups [9–13] have succeeded in obtaining an eight-membered ring system by RCM methodology. In our preliminary investigation [4], the cyclization of a diene **5** to eight-membered ring system was not successful. However, heating the reaction of **5** with **B** (25 mol%) at 50 °C gave **9** in 45% yield (Entry 5). Lactam **6** was then successfully converted to (−)-coniceine (**11**), the simplest indolizidine alkaloid *via* stepwise reductions as shown in Scheme 1.

3. Azacycloundecenes, toward manzamine C and its oxoanalogues [5c]

Manzamine C (**12**) is the simplest congener of manzamine alkaloids and bears an unprecedented azacycloundecene ring [14] The total synthesis of **12** was first achieved by us (Scheme 2) [15] and afterward by Gerlachs' group [16a] and Langlois' group [16b] using their own original methods. In our synthesis of **12** and *trans*-manzamine C (**13**),

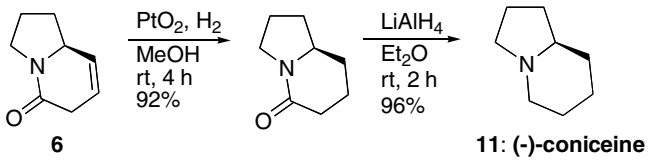
Table 1
Construction of chiral cycloalkanopyrrolidines using RCM



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	Concentration (mM)	Temperature (°C)	Time	Yield product (%)
1	**1**	**A** (5)	Benzene	20	rt	3 d	**6**, 93
2	**1**	**B** (5)	Benzene	20	rt	18 h	**6**, 66
3	**2**	**B** (5)	Benzene	20	rt	4 d	**7**, 73
4	**4**	**B** (5)	Benzene	20	50	3 h	**8**, 30
5	**5**	**B** (25)	CH_2Cl_2	2	50	20 h	**9**, 45



Scheme 1. Synthesis of (−)-coniceine.

cis and *trans* azacycloundecenes were key intermediates, which were prepared by conventional methods (Scheme 2). We have also successfully developed an efficient synthetic route to the saturated congener **14** to study the structure–activity relationship [17]. 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 (Figs. 3 and 4).

The formation of 11-membered rings by RCM is unusual [1f]. Recently Jean-Pierre Gesson reported successful RCM to 11-membered lactones from carbohydrate derivatives [18]. As shown in Scheme 2, 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 **B** in CH_2Cl_2 (20 mM) converted **18** to a single isomer of a cyclized product (16% yield) as a single isomer, which was identified as the *E* isomer **17** by comparison with an authentic sample prepared previously [15], together with dimeric products. On the other hand, the similar reaction of **18** in diluted solution (2 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 mixture was heated at 50 °C (Entry 3).

We were interested in the biological activity of an oxygen-functionalized analogue (**19**), which was expected to have higher solubility 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 (three steps).

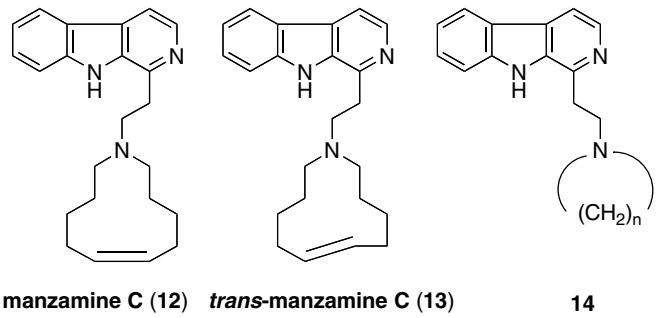


Fig. 3. Structure of manzamine **C**.

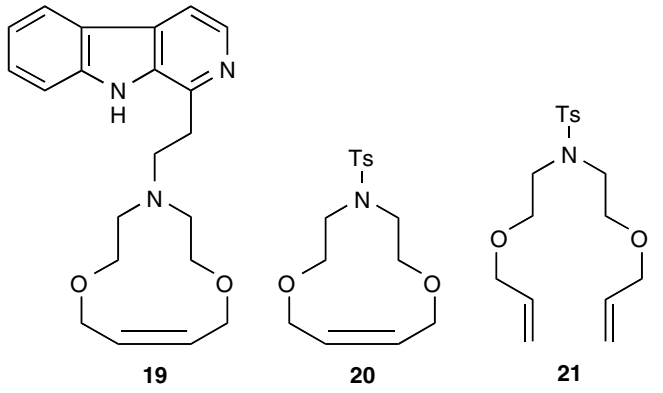
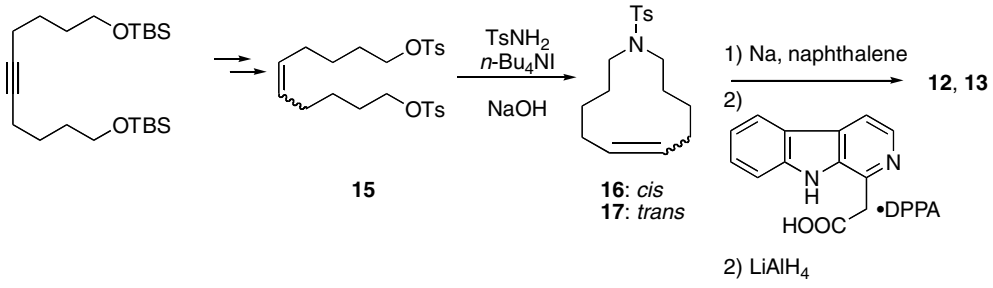


Fig. 4. Structure of oxo-manzamine **C**.

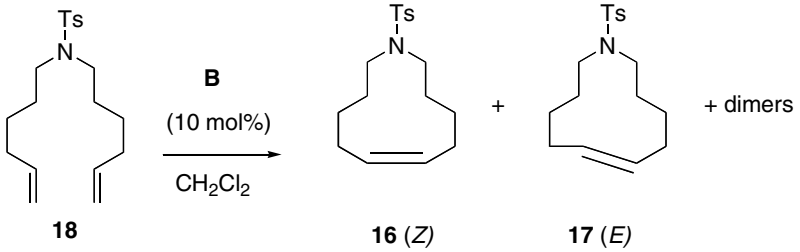
Reaction of **21** in 20 mM solution of CH_2Cl_2 or benzene using 10 mol% of **B** gave dimeric compound **22** (62–67%) and the desired *Z*-cycloundecene **20** (11–25%) (Table 3, Entries 1 and 2).

Under more diluted conditions, in 2 mM solution, **20** became the main product (53%, Entry 3). The yield of **20** did not increase even at an elevated temperature. The structure of **20** was determined by X-ray analysis. In contrast to **18**, the similar reaction of **21** gave only *Z* isomer **20** and *E*-isomer was not formed, presumably 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.



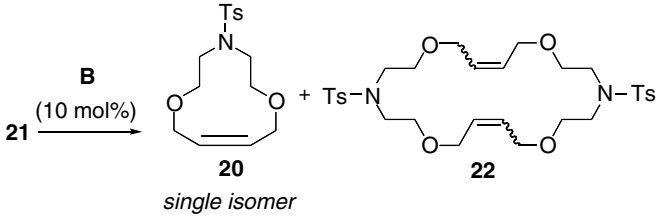
Scheme 2. Synthesis of azacycloundecene.

Table 2
RCM construction of cycloundecen



Entry	Substrate concentration (mM)	Temperature (°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

Table 3
RCM: construction of oxygen containing cycloundecen



Entry	Solvent	Substrate concentration (mM)	Temperature (°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

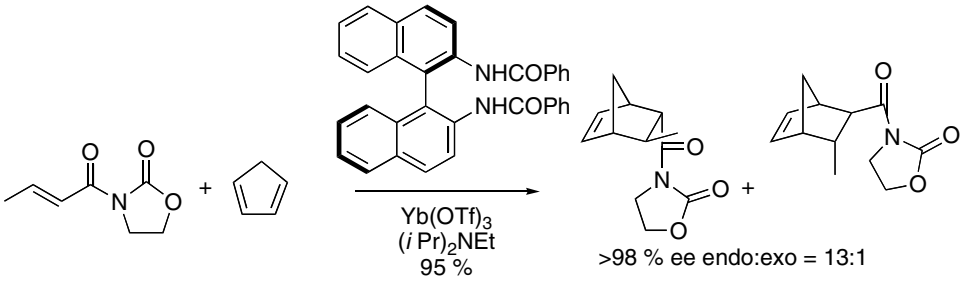
4. Axially chiral macrolactams [5d,5g]

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 (Scheme 3) [19].

1,1′-(2,2′-Bisacylamino)binaphthalenes (**23**–**25**) were synthesized by the reaction of chiral binaphthyldiamine with mixed anhydride of the corresponding acid, which then treated with ruthenium–carbene catalyst (**B**) under various conditions (Table 4).

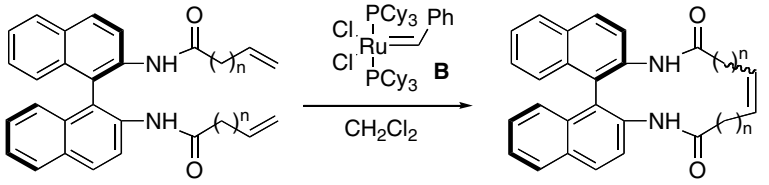
Initial experiments were conducted on **23** in CH_2Cl_2 (34 mM) with Grubbs' catalyst **B** (10 mol%) at room temperature. Although the yield was low, macrolactam **26** was obtained as a single isomer, which was assigned to be *E* on the basis of its X-ray analysis. Diluted and elevated temperature (50 °C) conditions using 30 mol% of **B** 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 at 50 °C 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). Under diluted conditions, the yield of **27** was increased to 89% (Entry 4). RCM of **24** occurs most efficiently in CH_2Cl_2 at refluxing temperature using 5 mol% of **B** (Entry 5).



Scheme 3. Diels–Alder reaction using chiral BINAMIDE.

Table 4
RCM of bisacylamino binaphthalenes

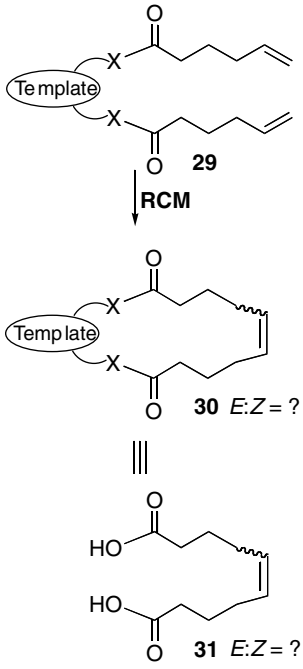


23: n = 2, **24**: n = 3, **25**: n = 4 **26**: n = 2, **27**: n = 3, **28**: n = 4

Entry	Substrate	Catalyst (mol%)	Concentration (mM)	Temperature (°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	$E/Z = 4.7/1$

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 [20,21]. In the RCM of dienes **23** and **25** to the corresponding 14-membered lactam **26** and an 18-membered lactam **28**, *E*-isomers are the major products. On the other hand, the RCM of **24** to a 16-membered ring lactam **27**, gave a *Z*-isomer as the major product (Table 4). As shown in Scheme 4, 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 [22]. 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 desired isomer could be obtained as a major product.



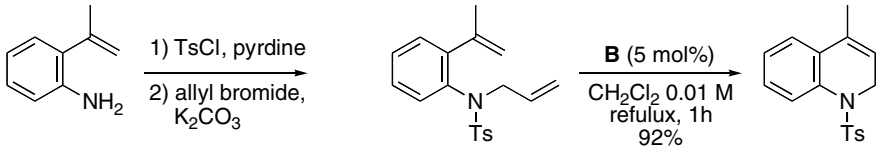
Scheme 4. Synthesis of dihexenoyl derivatives.

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 ligand for asymmetric reactions.

5. 1,2-Dihydroquinolines

Quinolines are a major class of alkaloids and play an important role in the fields of natural products and medicinal chemistry, although quinolines play a relatively minor role in fundamental metabolism. Several methods for synthesizing quinoline have been known since the late 1800s. However, despite of 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 [23].

In our continuing study of the RCM reaction and our approaches to the synthesis of novel anti-malarial agents



Scheme 5. Synthesis of 1,2-dihydroquinoline using RCM.

[24], 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 to give an excellent yield of 1,2-dihydroquinolines. This process leads to spontaneous air oxidation to quinoline after deprotection. We also describe its application to the synthesis of key intermediates for anti-malarial agents, such as quinine, chloroquine, and PPMP-quinine hybrid and total synthesis of augustureine.

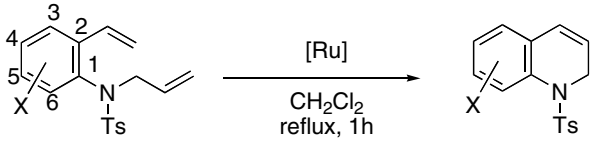
We first investigated RCM conditions for α,ω-diene **32** derived from commercially available 2-isopropenylaniline (Scheme 5). When **32** was treated with 5% of catalyst **B** in CH_2Cl_2 at refluxing temperature for 1 h, the corresponding 1,2-dihydroquinoline **33** was obtained in 92% yield.

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 **C** (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. 1,2-Dihydroquinolines could be readily converted to quinolines or 1,2,3,4-tetrahydroquinolines. In addition, the substituent on nitrogen is not limited to a *p*-toluenesulfonyl group. Having established the RCM conditions, we next examined the effect of protecting groups on nitrogen. Acetyl, benzyl and *tert*-butoxycarbonyl derivatives also gave the corresponding 1,2-dihydroquinolines [5k]. Dienes **44a**–**44c**, which were readily prepared from the commercially available *o*-aminostyrene, were reacted with both catalysts **B** and **C**. The reaction of *N*-benzyl derivative **44a** with catalyst **B** gave **45a** in excellent yield (Table 6, Entry 1), while *N*-acetyl derivative **44b** did not give the desired cyclized product (Entry 2). In this case, catalyst **B** probably reacted with the terminal double bond in **44b** to form a chelated intermediate **47**, which prohibited further RCM. When *N*-*tert*-butoxycarbonyl derivative **44c** was treated with catalyst **B** under similar conditions, 1,2-dihydroquinoline **45c** was obtained in modest yield. On the other hand, with catalyst **C**, the yields of **44b** and **44c** dramatically increased and the corresponding 1,2-dihydroquinoline, **45b** and **45c** were obtained in almost quantitative yields (Entries 3 and 5). The protective groups on nitrogen of products **45a**–**c** were readily removed during silica gel column chromatography to give 1,2-dihydroquinolines, which were spontaneously autooxidized to give 4-methylquinoline **46** quantitatively.

We next investigated a similar RCM for medium-sized rings such as in benzoazepine and benzoazocine. Dienes **48** and **49** were subjected to the above reaction conditions using both Grubbs' catalysts **B** and **C**. The reaction of **48** and **49** in the presence of catalyst **B** gave only the dimeric products **50** and **52**, respectively. In sharp contrast, the corresponding benzoazepine **51** and benzoazocine **53** were obtained with catalyst **C** in excellent yields (Table 7). The dimers **50** and **52** were cyclized to **51** (5 h, 98%) and **53** (6 h, 97%), respectively, by further treatment with the catalyst **C** under similar conditions.

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

35

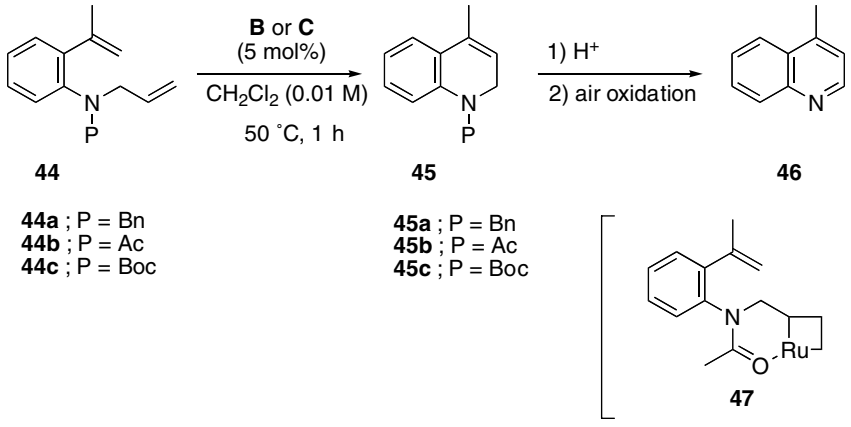
Entry	Substrate	[Ru]	Yield (%)
1	**34a**	**C**	93
2	**34b**	**C**	100
3	**34c**	**C**	90
4	**34d**	**B**	95
5	**34e**	**C**	74
6	**34f**	**B**	90
7	**34g**	**C**	87
8	**34h**	**C**	100
9	**34i**	**B**	90
10	**34j**	**C**	100
11	**34k**	**C**	95
12	**34l**	**C**	100

5.1. Silyl-enol ether ene metathesis [5f]

Many quinoline alkaloids which show important bioactivities, such as quinine and chloroquine, contain substituents at the 4-position. Therefore, we next focused our attention 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).

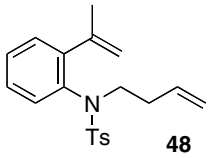
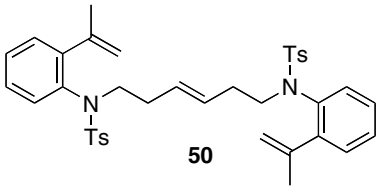
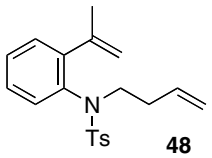
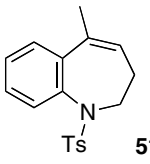
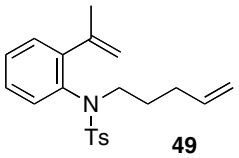
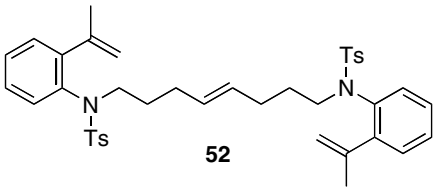
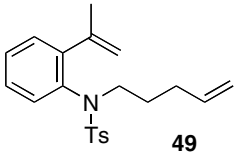
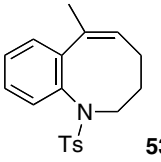
Enol methyl ether **54a** and enol silyl ether **54b** were prepared from commercially available *o*-aminoacetophenone

Table 6
Effect of protective groups on nitrogen



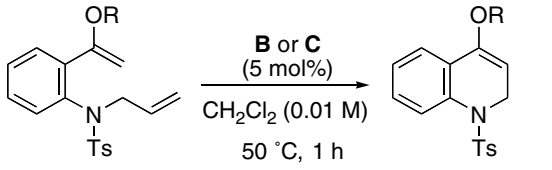
Entry	Substrate	Ru-catalyst	Product (%)
1	**44a**	**B**	**46** (95)
2	**44b**	**B**	**46** (0)
3	**44b**	**C**	**46** (98)
4	**44c**	**B**	**46** (63)
5	**44c**	**C**	**46** (97)

Table 7
Effect of Ru-catalysts on the RCM of dienes **48** and **49**

Entry	Substrate	Ru-catalyst	Product	Yield (%)
1		**B**		100
2		**C**		100
3		**B**		95
4		**C**		99

and subjected to our reaction conditions using catalysts **B** and **C**. When enol methyl ether **54a** and enol silyl ether **54b** were treated with **B**, the cyclized product was not obtained at all and the starting materials were recovered (Entries 1 and 3). In contrast, treatment of the same substrates with catalyst **C** gave the corresponding

Table 8
Effect of Ru-catalyst on the ene–enol metathesis of **54a** and **54b**



54a ; R = Me
54b ; R = TBS

55a ; R = Me
55b ; R = TBS

Entry	Substrate	Ru-catalyst	Concentration (M)	Product (%)
1	**54a**	**B**	0.01[a]	**55a** (0)
2	**54a**	**C**	0.01[a]	**55a** (95)
3	**54b**	**B**	0.01[a]	**55b** (0)
4	**54b**	**C**	0.01[a]	**55b** (95)
5	**54b**	**C**	0.01[b]	**55b** (99)
6	**54b**	**C**	0.1[a]	**55b** (96)
7	**54b**	**C**	0.1[b]	**55b** (97)

[a] Degassed conditions.
[b] Without degassing.

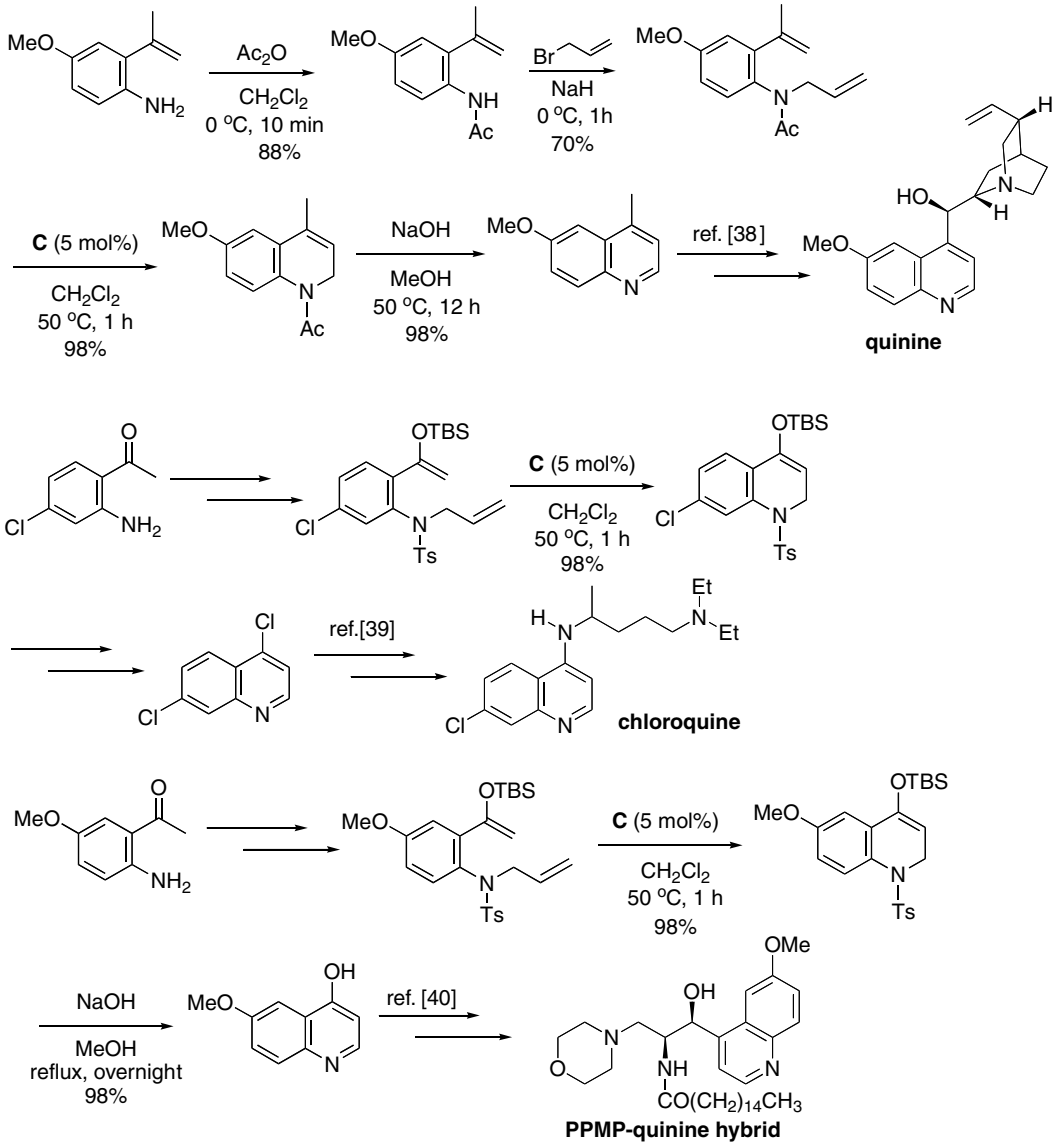
4-methoxy-1,2-dihydroquinoline **55a** and 4-siloxy-1,2-dihydroquinoline **55b** in 95% yield, respectively (Entries 2 and 4). This novel synthetic method could be applied to large-scale, multigram, syntheses.

5.2. Formal synthesis of chloroquine, quinine, PPMP-quinine hybrid [5k]

Encouraged by these results, we applied this novel method to the synthesis of key intermediates of anti-malarial agents, such as quinine [25], chloroquine [26], and PPMP-quinine hybrid [24], which are shown in Scheme 6.

5.3. Total synthesis of angustureine and determination of its absolute stereochemistry [5n]

A novel 2-substituted quinoline alkaloid, angustureine, was isolated from *Galipea officinalis* Hancock by Jacque-



Scheme 6. RCM based preparation of key intermediate for quinine, chloroquine and quinine-PPMP hybrid. See above-mentioned references for further information.

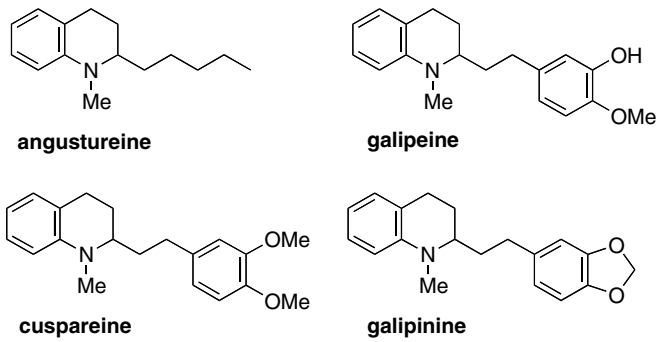


Fig. 5. Structures of 2-substituted quinoline alkaloids with anti-malarial activity isolated from *Galipea offinalis*.

mond-Collet et al. in 1999 [27]. The same plant has previously investigated and 5 quinoline alkaloids have already reported by Rakotoson et al. in 1998 [28]. 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 which were formerly reputed in folk medicine as bitter tonic in dyspepsia, dysentery and chronic diarrhea and for against fever long time ago [29]. The ethanolic extract from the bark of *G. officinalis*, called angostura, possessed the activity against *Mycobacterium tuberculosis* [30]. Recently, the anti-malarial and cytotoxic activities of angusturiene, galipeine, cuspareine and galipinine are also reported (Fig. 5) [31].

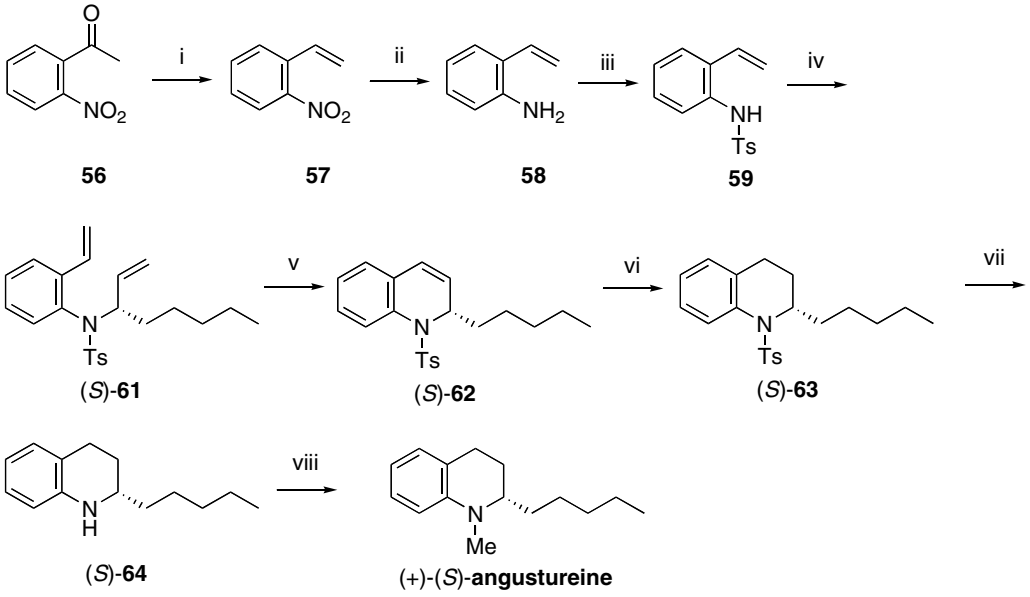
Although angustureine is isolated from the bark (980 mg from 1 kg of dried bark), its absolute configuration has not known when we started this research project [27]. During our synthetic study, Wang and coworkers reported synthesis of angustureine using iridium-catalyzed hydrogenation [32]. Our independent and original synthesis of optically pure (+)-(*S*)-angusturiene is shown in Scheme 7 and we determined the absolute configuration of natural product, angustureine, to be (−)-*R*.

We started the synthesis of angusturiene with Wittig olefination of readily available 2-nitrobenzaldehyde **56** to styrene **57** followed by reduction of **57** with Zn to give aniline **58**, which was protected as a tosylate **59**.

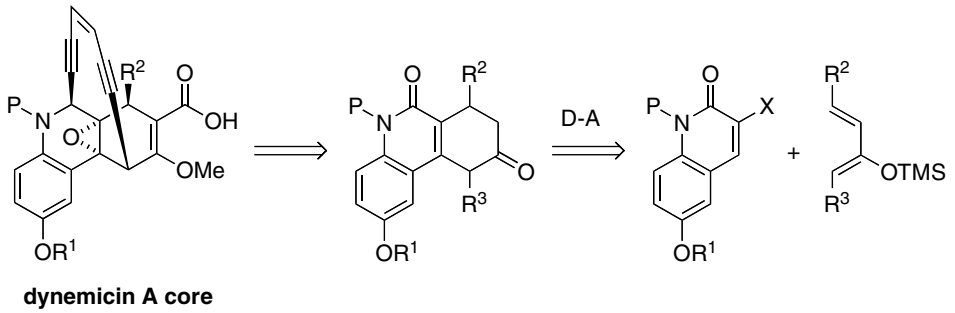
Installation of C-2 side chain was succeeded by employing Mitsunobu reaction as the first key step with readily available (*R*)-alcohol **60** in the presence of DEAD and PPh_3 to give desired chiral α,ω-diene **61** in 78% yield, 99% ee [33]. With (*S*)-**61** in hand, the key cyclization by RCM succeeded to give 1,2-dihydroquinoline **62** using catalyst **C** (0.01 M in CH_2Cl_2 50 °C for 1 h). The corresponding 1,2-dihydroquinoline was obtained in 92% yield. Subsequent catalytic hydrogenation of **62** with Adam's catalyst gave tetrahydroquinoline **63** in 94% yield, followed by detosylation resulted in the formation of tetrahydroquinoline **64** quantitatively. Finally, methylation of free nitrogen enabled the completion of (+)-(*S*)-angusturiene synthesis in 80% yield. The HPLC analysis indicated synthetic (+)-(*S*)-angusturiene has 94% ee, $[\alpha]_D^{23} = +7.91$ ($c = 1.00$, $CHCl_3$), $[\alpha]_D^{26} = +4.35$ (c 1.00, $CHCl_3$); $[\alpha]_D^{26} = +5.18$ (c 1.00, MeOH); $[\alpha]_D^{26} = +5.10$ (c 1.00, EtOH). The reported $[\alpha]_D$ is −7.61 [27] Therefore, the absolute configuration of angusturiene was confirmed to be *R*-configuration.

5.4. 2-Quinolinone [5p]

2-Quinolones are valuable intermediates in organic synthesis [34] 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 synthetic

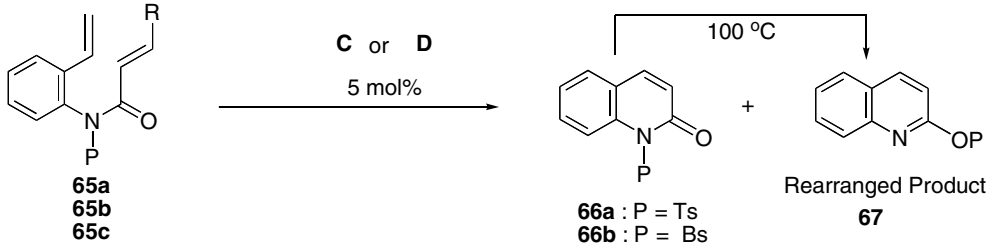


Scheme 7. Synthesis of angusturiene: (i) Ph_3PMeBr, $KN(TMS)_3$, THF, 20 °C, 1 h 90%; (ii) Zn powder, AcOH, 20 °C, 2 h, 68%; (iii) TsCl, pyridine, CH_2Cl_2, 20 °C, 1 h, 86%; (iv) (*R*)-(−)-1-octen-3-ol(**60**), DEAD, PPh_3, THF, 20 °C, 2 h, 78%; (v) Ru catalyst **C**, CH_2Cl_2 0.01 M, 50 °C, 1 h, 92%; (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%.



Scheme 8. Diels–Alder reaction for dynemicin A core.

Table 9
Preparation of *N*-sulfonyl-2-quinoline



Entry	Substrate			Catalyst	Conditions			Product (%)	Remark
		R	P		Temperature (°C)	Solvent	Time (h)		
1	**65a**	H	Ts	**C**	50	CH_2Cl_2	1	NR	–
2	**65a**	H	Ts	**D**	50	CH_2Cl_2	1	**66a** (trace)	–
3	**65a**	H	Ts	**D**	100	Toluene	4	**66a** (56)	Rearrange 32%
4	**65a**	H	Ts	**D**	80	Toluene	4	**66a** (95)	–
5	**65b**	Me	Ts	**D**	80	Toluene	4	**66a** (74)	STM 20%
6	**65c**	H	Bs	**D**	80	Toluene	5	**66b** (90)	–

study of dynemicin A [35], we found that *N*-protected-2-quinolinone derivatives are good dienophiles for the Diels–Alder reaction (Scheme 8). Theoretically, *N*-sulfonyl-2-quinolinones are better dienophiles than *N*-methoxycarbonyl or *N*-methoxymethyl derivatives. However, we could not obtain *N*-sulfonyl-2-quinolinones by direct sulfonylation of 2-quinolinones.

The requisite dienes (**65**) were prepared by condensation of the corresponding *N*-protected *O*-vinyl aniline and acid chloride. When catalyst **C** was used for RCM of **65a** under the standard conditions, no cyclized product was obtained and the starting material was recovered unchanged (Table 9, Entry 1). Thus, instead of catalyst **C**, catalyst **D** was used under the same reaction conditions. But, **66a** was obtained in trace amounts. When the reaction temperature was raised to 100 °C, **66a** was obtained in 56% yield, accompanied with rearranged product **67** was also obtained in 32% yield (Entry 3). As shown in entry 4, at 80 °C, the desired **66a** was formed in quantitative yield. 2-Quinolone **66** thermally arranged to **67** at 100 °C quantitatively without any catalyst. Compound **67** should be a useful substrate for the synthesis of various 2-substituted quinoline derivatives.

N-Crotonoyl-*N*-tosylaminostyrene **65b** and **65c** also provided the corresponding RCM products **66a** (Entry 5) and **66b** (Entry 6), respectively.

Thus, the novel and efficient synthetic method for *N*-sulfonyl-2-quinolinone was achieved by RCM using a well-defined Hoveyda catalyst (**D**).

6. Indoles [5h]

Indoles are probably the most widely distributed heterocyclic compounds in nature and play an important role in metabolism. Indole derivatives are also very important molecules in medicinal and organic chemistry. Therefore, a variety of synthetic method for indole ring have developed since the 1800s. However, a practical preparation of substituted indoles is still a challenging subject in the area of heterocyclic chemistry [36].

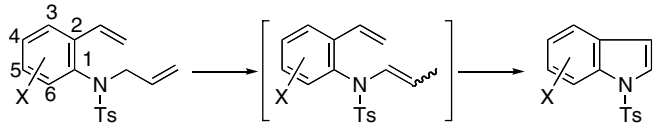
Isomerization of olefin proceeded under acidic, basic or photochemical conditions has been known to give a mixture of olefins that depends on their thermodynamic stability. Recent advances in transition-metal chemistry (Fe, Pd, Rh, Pt, Ni, Ir, Ru, Co and Cr) have enabled milder conditions for olefin isomerization to realize selective and

synthetically useful transformations such as deprotection of an allyl group on nitrogen and oxygen functionalities [37]. Very recently, a few reports have appeared concerning this olefin isomerization using a ruthenium-carbene catalyst, such as the Grubbs catalyst. Such isomerization is limited to substrates which contain an oxygen or a nitrogen substituent in the olefinic side-chain. In addition, the reaction competes with metathesis [1].

We found a novel method for synthesizing substituted quinolines by RCM including silyl-enol ether ene metathesis [5f]. These previous results prompted us to investigate cross-metathesis to prepare a silyl-enol ether. Unexpectedly, however, we found selective isomerization of the terminal olefin to the corresponding internal olefin, which made possible a novel indole synthesis by subsequent RCM. We report here a selective isomerization of a terminal olefin by combining a ruthenium-carbene catalyst with vinyloxytrimethylsilane, and its application to the synthesis of an indole ring from 2-(*N*-allylamino)styrene by RCM.

We carried out the isomerization of **34a** (Table 10) in competition with RCM. While the reaction of **34a** with ruthenium catalyst **B** gave 1,2-dihydroquinoline (**35a**) quantitatively [5f], in sharp contrast, in the presence of vinyloxytrimethylsilane (**70**, 1 eq. is sufficient for this substrate) the reaction of **34a** with catalyst **B** afforded enamine (**68a**) in quantitative yield, which was inaccessible by other conventional methods. Although the use of a ruthenium-carbene catalyst in the isomerization of olefin has been reported, [37m–o] to the best of our knowledge, this is the first example of a highly selective isomerization using a ruthenium-carbene complex that proceeds faster than RCM.

Table 10
Synthesis of indole 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

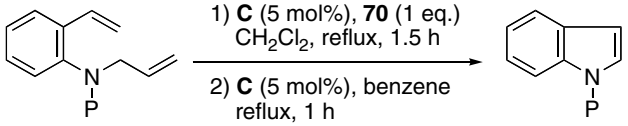
68 quant.

69

Entry	Substrate	Yield (%), Reaction conditions[a] **69**
1	**34a**	94, I then III(1)
2	**34b**	83, I then III(1)
3	**34c**	96, I then IV[b](16)
4	**34d**	100, I then III(3)
5	**34e**	54, I then IV[c] (32)[d]
6	**34f**	83, I then IV(17)
7	**34g**	85, I then IV(4, 5)
8	**34h**	79, I then IV(13)
9	**34i**	86, I then IV(2)
10	**34j**	33, I then IV[c](24)[e]
11	**34k**	20, I then IV[c](24)[f]
12	**34l**	77, I then III(1)

[a] I: **C** (5 mol%), **70** (1 eq.), CH_2Cl_2, reflux, 1.5 h, II: **C** (5 mol%), **70** (1 eq.), CH_2Cl_2, reflux, 4 h, III: **C** (5 mol%), benzene, reflux, reaction time is indicated parenthesis, IV: **C** (5 mol%), degassed toluene, reflux, reaction time is indicated parenthesis.
[b] 10 mol% of **C** was employed.
[c] 20 mol% of **C** was employed.
[d] Enamide was also obtained in 46% yield.
[e] Enamide was also obtained in 67% yield.
[f] Enamide was also obtained in 80% yield.

Table 11
Indole synthesis: substituent effect on nitrogen



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

69

Entry	Substrate	Yield (%) **69**
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.

Since this novel method is quite effective for generating enamine, we next applied this reaction to the synthesis of indole. The crude enamine **68a**, which was obtained by the evaporation of volatile material after the isomerization of **34a** as described above, was subjected to normal RCM conditions using catalyst **C** at 80 °C in benzene. As a result, the expected indole (**69a**) was isolated in 94% yield. Similarly, **34b**–**34l** gave **69b**–**69l** *via* isomerized enamine **68b**–**68l**, respectively.

The effect of the substituent on nitrogen was examined and the results are shown in Table 11. Not only *p*-toluenesulfonyl, but also acetyl, benzoyl,*tert*-butoxycarbonyl, benzyloxycarbonyl and methanesulfonyl derivatives gave corresponding indoles (**69**) *via* enamides (**68**).

7. Conclusion

We have developed silyl-enol ether ene metathesis and selective isomerization of terminal olefin using ruthenium–carbene catalyst and established novel preparative method for nitrogen-containing heterocycles. We also applied this method for the synthesis of (−)-coniceine, (*S*)-pyrrolam A and angustureine and the absolute configuration of angustureine was determined.

Acknowledgements

It is with great pleasure that we acknowledge all coworkers of this project, whose names are written in Ref. [5].

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