JOC Article

Development of Isomerization and Cycloisomerization with Use of a Ruthenium Hydride with *N*-Heterocyclic Carbene and Its Application to the Synthesis of Heterocycles

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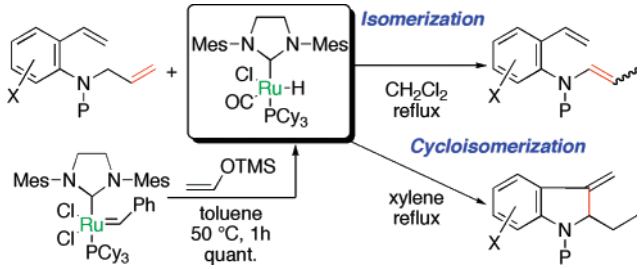

A pure ruthenium hydride complex with *N*-heterocyclic carbene (NHC) ligand was efficiently generated from the reaction of a second-generation Grubbs ruthenium catalyst with vinyloxytrimethylsilane and unambiguously characterized. This ruthenium hydride complex showed high catalytic activity for the selective isomerization of terminal olefin and for the cycloisomerization of 1,6-dienes. These reactions of *N*-allyl-*o*-vinylaniline lead to novel synthetic methods for heterocycles such as indoles and 3-methylene-2,3-dihydroindoles, which are useful synthons for bioactive natural products. These procedures address an important issue in diversity-oriented synthesis.

Introduction

Heterocyclic compounds are very beneficial compounds for human life, since they are components of natural products, including the human body, and exhibit a variety of notable pharmaceutical activities. Hence, numerous methods for the synthesis of heterocycles have been developed since the 1800s.[1] Remarkably, despite the considerable amount of effort that has been expended in this area, it is still a challenge to develop more efficient methodologies and strategies for producing heterocycles with the desired substituents and functional groups.[2]

On the other hand, metathesis was introduced in the 1950s, and has opened a new field of organic chemistry. Recent Ru catalysts (**A**[3], **B**,[4] **C**,[5] and **D**,[6] Figure 1) which were developed by Grubbs, Hoveyda, and their respective co-workers are suitable for a variety of functional groups, easy to handle, and, moreover, commercially available.[7]

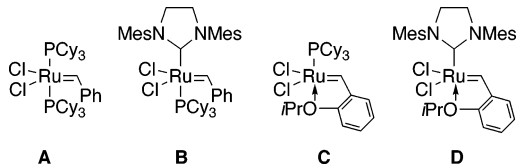

FIGURE 1. Ruthenium carbene catalysts.

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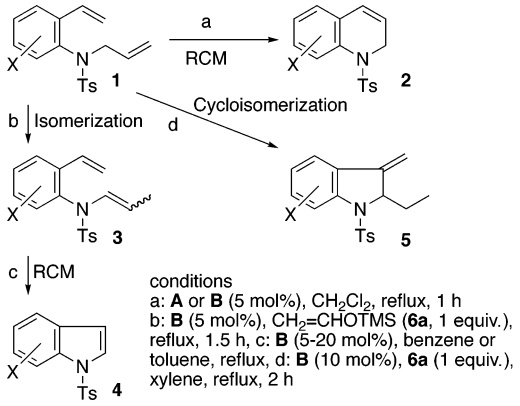
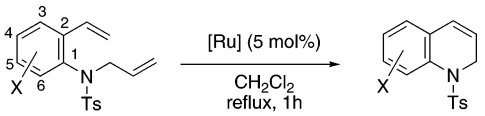
SCHEME 1. Synthesis of 2, 4, and 5 from 1



Nonmetathetic catalytic activity has recently been identified, and has increased the utility of these catalysts beyond metathesis.[8]

We have been investigating the feasibility of using metathesis to prepare heterocyclic compounds and its application to the synthesis of bioactive natural products.[9] Recently, we found that *N*-allyl-*o*-vinylaniline (**1**) gave 1,2-dihydroquinoline (**2**) by normal RCM, and developed silyl enol ether−ene metathesis for the novel synthesis of 4-silyloxy-1,2-dihydroquinoline, and thus demonstrated a convenient entry to quinolines and 1,2,3,4-tetrahydroquinolines.[9f,k] We also found a novel selective isomerization of terminal olefins and a cycloisomerization of 1,6-dienes, using ruthenium carbene catalyst and silyl enol ether, which represented a new synthetic route to a series of substituted indoles (**4**) and 3-methylene-2,3-dihydroindoles (**5**).[9h,l] We now report our systematic studies on RCM, effective isomerization followed by RCM, and cycloisomerization of **1**, including the scope and limitations of these reactions. Substituted **2**, **4**, and **5**, which are useful synthons for biologically active natural products, were selectively synthesized from **1** with catalyst **B** by slightly changing the reaction conditions (Scheme 1). Cycloisomerization of **1** efficiently gives 2,3-disubstituted indole, and **5**. We also report an unambiguous characterization of intervenient ruthenium hydride complex with *N*-heterocyclic carbene (NHC) ligand, which is generated from **B** and vinyloxytrimethylsilane (**6a**) and the actual active species for these nonmetathetic reactions, isomerization of a terminal olefin, and cycloisomerization of an α,ω-diene. Olefin isomerization of Grubbs catalyst has been reported and has been exploited recently in a deprotection of allyl ethers and amines. Unfortunately, the ruthenium species derived from the decomposition of the Grubbs catalyst (**B**) responsible for this reactivity has been unclear.[10]

TABLE 1. Synthesis of 1,2-Dihydroquinoline (2) from 1



1a: H, **1b**: 6-OMe, **1c**: 5-OMe
1d: 4-OMe, **1e**: 3-OMe
1f: 4,5,6-triOMe, **1g**: 6-Cl
1h: 5-Cl, **1i**: 4-Cl, **1j**: 3-Cl
1k: 3-Me, **1l**: 6-Me

2

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

Results

RCM of 1 to Substituted 1,2-Dihydroquinoline (2). The reaction of **1a**−***l*** with **A** or **B** (5 mol %) in refluxing CH_2Cl_2 for 1 h gave the corresponding 1,2-dihydroquinolines (**2a**−***l***) via RCM in good to excellent yields (Table 1) 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. Acetyl, benzyl, and *tert*-butoxycarbonyl derivatives also gave the corresponding 1,2-dihydroquinolines.[9k] With this method, an anti-malarial compound, (+)-(*S*)-angustureine, was synthesized efficiently and the absolute configuration of natural angustureine was established to be (−)-(*R*)-enantiomer.[9m]

Isomerization and Subsequent RCM of 1 to Substituted Indole 4. On the basis of our finding of silyl enol ether−ene ring-closing metathesis, we applied this reaction to a cross metathesis. The reaction of terminal olefin **7** with **B** exclusively gave the dimeric compounds **9**, which is the homo cross metathesis product of **7** (Table 2, entry1).

However, when the reaction of **7** with **6a** was carried out, the isomerization product **8** was unexpectedly obtained in 74%

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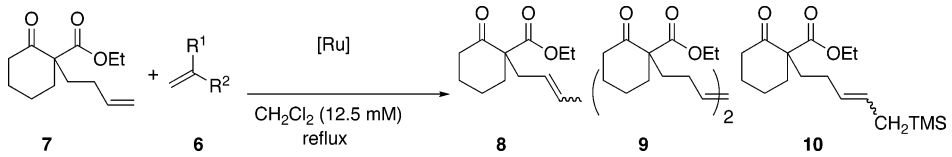
TABLE 2. Reaction of 7 with B in the Presence of Electron-Rich Olefins



7 6 8 9 10

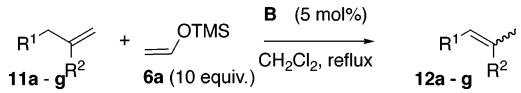
entry	6	R1	R2	equiv.	[Ru] (mol %)	time (h)	product (%)	*E*/*Z* ratio of **8**[a]
1[b]				0	**B** (5)	23	**9** (98)	
2	**6a**	OTMS	H	2	**B** (5)	20	**8** (74[a])	3.2/1
3	**6b**	OTBS	Ph	2	**B** (5)	3	**9** (84)	
4	**6c**	OTMS	Me	2	**B** (5)	88	**9** (80)	
5	**6d**	CH_2TMS	H	2	**B** (5)	16	**9** (44), **10** (48)	
6	**6a**	OTMS	H	4	**B** (5)	20	**8** (83[a])	3.5/1
7	**6a**	OTMS	H	10	**B** (5)	24	**8** (94)	3.3/1
8	**6a**	OTMS	H	10	**B** (5)	3	**8** (100)	3.5/1
9	**6a**	OTMS	H	10	**B** (2.5)	24	**8** (81)	2.6/1
10	**6a**	OTMS	H	10	**B** (1)	24	**8** (50[a])	nd
11	**6a**	OTMS	H	10	**B** (0)	11	**8** (0[c])	
12	**6a**	OTMS	H	10	**A** (5)	24	**8** (0[c])	
13	**6a**	OTMS	H	10	**C** (5)	24	**8** (75)	4.0/1
14	**6a**	OTMS	H	10	**D** (5)	25	**8** (70)	2.7/1
15	**6e**	OAc	H	10	**B** (5)	24	**8** (0[c])	
16	**6f**	OEt	H	10	**B** (5)	24	**8** (100)	3.2/1
17	**6f**	OEt	H	10	**B** (5)	3	**8** (12[a])	nd

[a] The ratio and yield were determined by ^{1}H NMR spectroscopy. [b] Reaction of **7** with **B** in the absence of **6**. [c] No reaction.

yield (entry 2). When some other electron-rich disubstituted terminal olefin (**6b** and **6c**) was used instead of **6a**, **8** was not formed, and instead **9** was obtained (entries 3 and 4), presumably due to steric hindrance of the substituents in the formation of the organometallic intermediate. Allylsilane (**6d**) did not give **8**, but gave only a mixture of **9** and CM product **10** in moderate yields (entry 5). The amounts of catalyst **B** and **6a** were examined and it became clear that 5 mol % of **B** and 10 equiv of **6a** were necessary for the isomerization of terminal olefins to internal olefins (entries 6−11). While the first-generation Grubbs catalyst (**A**) without a NHC ligand did not catalyze the isomerization, catalyst **B** with **6a** gave isomerization product in excellent yield (entries 7 and 12). Likewise, both first- and second-generation Hoveyda catalysts (**C** and **D**) in the presence of **6a** gave the corresponding isomerized product in reasonable yields, respectively (entries 13 and 14). When acetoxy vinyl (**6e**) or ethyl vinyl ether (**6f**) was used instead of **6a**, no reaction was observed or the reaction rate of isomerization became much slower, respectively (entries 7 and 8 vs 15−17). Both degassed solvent and nondegassed solvent gave similar results for isomerization of **7**. According to these results, other terminal olefins were subjected to our best isomerization conditions and all 1-monosubstituted olefins were converted to give the corresponding 2-alkenes (Table 3, entries 1−6), while 2,2-disubstituted olefin was recovered unchanged (entry 7). No further isomerization was observed in any of the runs examined. It has been previously reported that ruthenium carbene catalyst can isomerize terminal olefin, when the substrate does not allow metathesis.[10]

However, under our conditions, isomerization is more favorable than metathesis in a competitive reaction, even in such a case the substrates can easily give a metathesis product. This characteristic reaction is clearly demonstrated with *N*-allyl-*o*-vinylaniline (**1**). Through optimization of the amount of **6a** for **1a**, it became clear that 1 equiv of **6a** was sufficient to convert **1a** to enamide **3a** in excellent yield (Table 4).

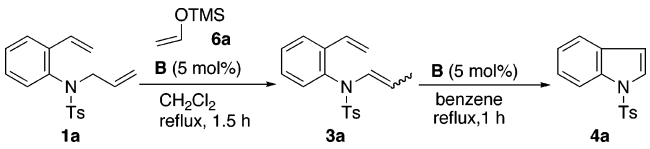
TABLE 3. Isomerization of Various Terminal Olefins (11)



entry	substrate	R1	R2	time (h)	yield (%)[a]	*E*/*Z*[b]
1	**11a**	Ph	H	1.5	quant (34)	12.8/1
2	**11b**	$PhCH_2$	H	3.0	58	2.8/1
3	**11c**	*p*-$MeOC_6H_4CH_2$	H	3.0	78	8.5/1
4	**11d**	$HO(CH_2)_3$	H	3.0	quant (34)	6.1/1
5	**11e**	$BnO(CH_2)_3$	H	3.0	quant (96)	8.2/1
6	**11f**	BnO	H	3.0	73	1/1.25
7	**11g**	$BnOCH_2$	CH_3	3.0	NR	

[a] NMR yield. Yields in parentheses indicate the isolated yields. [b] Determined by ^{1}H NMR.

TABLE 4. Optimization of the Amount of 6a for 1a

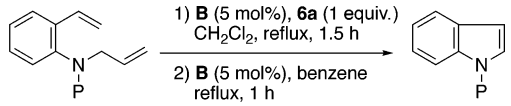


entry	**6a** (equiv.)	yield of **4a** (%)
1	10	quant.
2	5	90
3	2	96
4	1	94
5	0.1	nd[a]

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

Subsequent treatment of **3a** without purification obtained by evaporation of the volatile materials with **B** (5 mol %) in refluxing benzene for 1 h gave indole **4a** in quantitative yield. Indole synthesis has been the subject of intensive investigations, especially in the area of alkaloid synthesis as well as medicinal chemistry.[2] These results provide the first example of indole synthesis with RCM. The effect of the substituent on nitrogen

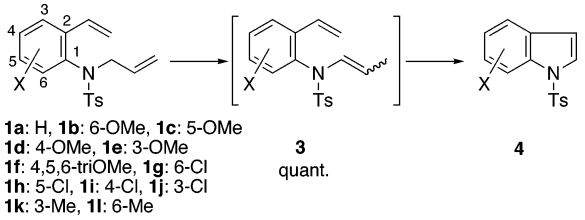
TABLE 5. Indole Synthesis: Substituent Effect on Nitrogen



entry	substrate	yield of **4** (%)
1	**1a**	94
2	**1m**	82
3	**1n**	86
4	**1o**	80
5	**1p**	86[a]
6	**1q**	75[b]

[a] Reaction time of RCM was 16 h. [b] 15% of **5q** was also obtained.

TABLE 6. Synthesis of Indole from 1



entry	substrate	yield of **4** (%), reaction conditions[a]
1	**1a**	94, I then III (1)
2	**1b**	83, I then III (1)
3	**1c**	96, I then IV[b] (16)
4	**1d**	100, I then III (3)
5	**1e**	54, I then IV[c] (32)[d]
6	**1f**	83, I then IV (17)
7	**1g**	85, I then IV (4.5)
8	**1h**	79, I then IV (13)
9	**1i**	86, I then IV (2)
10	**1j**	33, II then IV[c] (24)[e]
11	**1k**	20, I then IV[c] (24)[f]
12	**1*l***	77, I then III (1)

[a] I: **B** (5 mol %), **6a** (1 equiv.), CH_2Cl_2, reflux, 1.5 h. II: **B** (5 mol %), **6a** (1 equiv.), CH_2Cl_2 reflux, 4 h. III: **B** (5 mol %), benzene, reflux, reaction time is indicated in parentheses. IV: **B** (5 mol %), degassed toluene, reflux, reaction time is indicated in parentheses. [b] 10 mol % of **B** was employed. [c] 20 mol % of **B** 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.

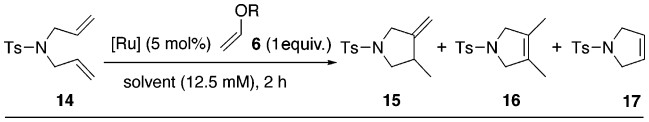
was examined and the results are shown in Table 5. Not only *p*-toluenesulfonyl, but also acetyl, benzoyl, *tert*-butoxycarbonyl, benzyloxycarbonyl, and methanesulfonyl derivatives gave corresponding **4** via **3**.

To clarify the scope and limitation of this indole synthesis, the effect of the substituent on the aromatic ring was examined and the results are summarized in Table 6. Under our optimized reaction conditions, **1a**−***l*** gave enamide (**3a**−***l***) quantitatively. Although substituents at the 3-position of **1**, such as in **1e**, **1j**, and **1k**, prevented the cyclization to give the corresponding indoles (entries 5, 10, and 11) probably due to steric and/or chelating effects, other substrates gave the corresponding RCM product in good to excellent yields.

Cycloisomerization of 1 to Substituted 3-Methylene-2,3-dihydroindole (5). The most plausible species formed by the reaction of terminal olefin with **6a** using **B** in situ is likely a ruthenium hydride that undergoes hydroruthenation followed by *β*-hydride elimination to give the corresponding isomer. On the basis of this hypothesis, the intermediate alkyl ruthenium complex of a diene could undergo intramolecular carboruthenation followed by *β*-hydride elimination to give a cyclic compound. Therefore, *N*,*N*-diallyl-*p*-toluenesulfonamide (**14**), which is frequently used in RCM and cycloisomerization studies, was subjected to our reaction conditions (Table 7). When **14** and **6a** were treated with 5 mol % of **B** at room temperature in CH_2Cl_2 for 2 h the expected cycloisomerized product **15** was obtained in 65% yield with RCM product **17** in 21% yield (entry 1). On the other hand, the same reaction at 40 °C gave a mixture of cycloisomerized products, **15** and **16**, in respective yields of 86% and 14% (entry 2). The yield of the thermodynamically stable compound **16** increased with an increase in the reaction temperature. In contrast to the selective isomerization of terminal olefin, ruthenium complexes **B** and **D** were more active in cycloisomerization than **A** and **C**, as shown in Table 7. Therefore, the existence of the NHC ligand is critical for cycloisomerization (entries 2, 5, 6, and 7). A combination of **B** and **6f** required a longer reaction time than **6a** (entries 8 and 9). Although **B** catalyzed the isomerization of **15** to **16**, the presence of **6a** promoted this reaction more efficiently (Table 8). The isomerization of **16** to **15** was not detected under similar conditions (Scheme 2).

On the basis of these results, we envisioned that the cycloisomerization of **1** might proceed at higher temperature. As shown in Table 9, the reaction of **1a** and **6a** with **B** gave **3a**

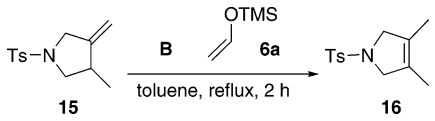
TABLE 7. Reaction of *N*,*N*-Diallyl-*p*-toluenesulfonamide 14



entry	[Ru]	**6**	R	solvent	temp (°C)	yield (%)[a] **15**	**16**	**17**	recovery of **14** (%)
1	**B**	**6a**	TMS	CH_2Cl_2	rt	65	0	21	0
2	**B**	**6a**	TMS	CH_2Cl_2	40	86	(14)	0	0
3	**B**	**6a**	TMS	benzene	80	43	56	0	0
4	**B**	**6a**	TMS	toluene	110	(22)	78	0	0
5	**A**	**6a**	TMS	CH_2Cl_2	40	10	0	59	28
6	**C**	**6a**	TMS	CH_2Cl_2	40	29	0	64	0
7	**D**	**6a**	TMS	CH_2Cl_2	40	71	24	0	0
8	**B**	**6f**	Et	CH_2Cl_2	40	37	0	5	58
9	**B**	**6f**	Et	toluene	110	52	46	0	0

[a] Yields in parentheses were estimated by ^{1}H NMR spectroscopy.

TABLE 8. Conversion of 15 to 16



entry	**B** (mol %)	**6a** (equiv.)	yield (%) **15** (recovery)	**16**
1	5	1	19	80
2	0	0	100	0
3	0	1	98	0
4	5	0	85	15

SCHEME 2. Conversion of 16 to 15

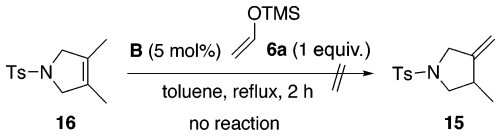
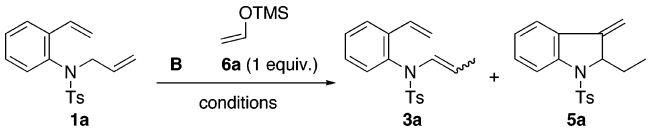


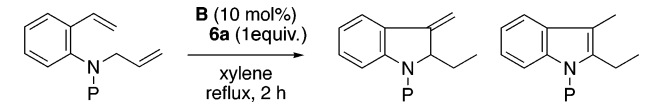
TABLE 9. Isomerization and Cycloisomerization of Diene 1a



entry	B (mol %)	conditions	yield (%)[a] 3a	5a
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 10. Cycloisomerization: Substituent Effect on Nitrogen



entry	substrate	yield of **5** and **13** (%) (ratio of **5**/**13**)
1	**1a**	81 (100/0)
2	**1m**	69 (57/43)
3	**1n**	86 (86/14)
4	**1o**	92 (84/16)
5	**1p**	99 (79/21)
6	**1q**	86[a] (100/0)

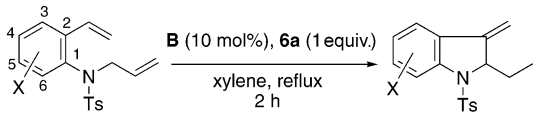
[a] 3 equiv of **6a** was used.

exclusively (entry 1). In contrast to the reaction in CH_2Cl_2, the same reaction in refluxing xylene gave **5a** as the major product (entry 4) together with **3a**. When 10 mol % of **B** was used, the yield of **5a** increased to 81%.

The effect of the substitutent at the nitrogen was examined and the results are summarized in Table 10. Acetyl, benzoyl, *tert*-butoxycarbonyl, benzyloxycarbonyl, and methanesulfonyl derivatives gave cycloisomerized products (**5** and **13**) in yields of 69−99%. Sulfonamides (**1a** and **1q**) gave indoline **5** in excellent yields. The reaction of methanesulfonyl derivative **1q** with 1 mol equiv of **6a** gave a mixture of **5q** (71%) and 1,2-dihydroquinoline (29%), indicating that 1 equiv of **6a** was not sufficient for the formation of **5q**. Consequently, the yield of **5q** increased to 86% with the use of 3 equiv of **6a** (entry 6). To determine the scope and limitations of the present catalytic reactions, the substituent effect was examined by using several substrates (**1a**−***l***), and some selected results are shown in Table 11. All of the substrates, except **1b**, **1f**, **1g**, **1*l***, which have a substituent at 6-position, gave cycloisomerized products in yields of 24−95%. This methodology was also extended to the construction of 3-methylene-2,3-dihydrobenzofuran (**19a**−**c**). As shown in Table 12, when *O*-allyl-*o*-vinylphenol derivatives (**18a**−**c**) were refluxed in toluene with **B** and **6a**, **19a**−**c** were obtained in reasonable yields, except that **18d** gave only isomerization product in low yield and **18d** was recovered in 62% yield. The results with **1b**, **1f**, **1g**, **1*l***, and **18d** suggest that chelation between the ortho 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

TABLE 11. Synthesis of Indoline from 1



1a: H, **1b**: 6-OMe, **1c**: 5-OMe
1d: 4-OMe, **1e**: 3-OMe
1f: 4,5,6-triOMe, **1g**: 6-Cl
1h: 5-Cl, **1i**: 4-Cl, **1j**: 3-Cl
1k: 3-Me, **1l**: 6-Me

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

[a] Enamide was obtained quantitatively.

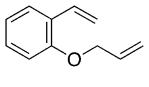
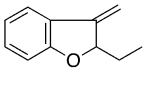
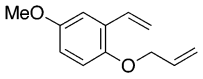
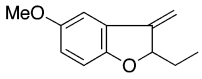
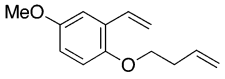
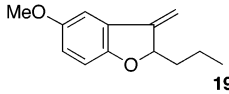
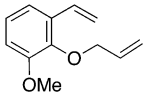
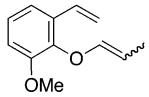
reactions of **1r**, **1s**, and **1t** were performed with 1 equiv of **6a** with **B** in refluxing xylene for 2 h (Table 13). Diene **1r** gave cycloisomerization product **5r** as the major product together with isomer **3r** (entry 1). Isomerization of **1s** gave **3s** in 32% yield together with unreacted **1s** (57%) (entry 2). Under the same conditions, the reaction of **1t** gave **3t** and **5t** in respective yield of 34% and 52% (entry 4). When enamides (**3s** and **3t**) were subjected to the same reaction conditions, the corresponding **5s** and **5t** were obtained in respective yields of 66% and 80% (entries 3 and 5), which shows that enamides **3** were intermediates for **5**. In contrast, the substrates in Figure 2 did not give a cycloisomerization product. The present cycloisomerization is general and useful for substrates with various functional groups.

Exomethylene in 3-methylene-2,3-dihydroindole has a very useful functional group for further transformation. Concerning this exomethylene group, Sakamoto[11a] and Boger[11b] have previously reported hydroboration to introduce a hydroxymethyl group, and we[11c] and Lectka[11d] prepared tryptophan and tryptamine derivatives using an imino−ene reaction. We also found that ozonolysis and RCM can be applied to this exomethylene, as shown in Scheme 3. Therefore, the cycloisomerization of *N*-allyl-*o*-vinylaniline (**1**) is a new method for the synthesis of 2,3-disubstituted indole derivatives.

Actual Active Species. All of the above methods for heterocycles, including RCM of diene, isomerization of terminal olefin, and cycloisomerization of diene, were easily carried out with use of 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 con-

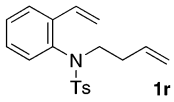
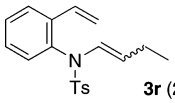
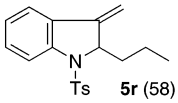
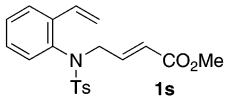
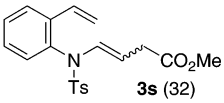
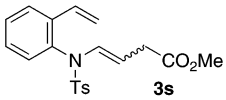
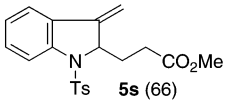
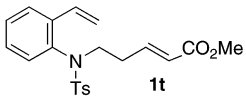
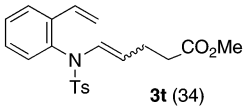
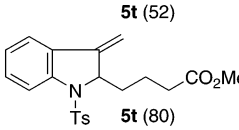
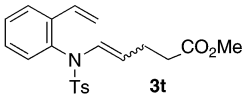
(11) (a) Sakamoto, T.; Kondo, Y.; Uchiyama, M.; Yamanaka, H. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1941−1942. (b) Boger, D. L.; Ishizaki, T.; Wysocki, R. J., Jr.; Munk, S. A. *J. Am. Chem. Soc.* **1989**, *111*, 6461−6463. (c) Yamanaka, M.; Nishida, A.; Nakagawa, M. *J. Org. Chem.* **2003**, *68*, 3112−3120. (d) Ferraris, D.; Young, B.; Cox. C.; Dudding, T.; Drury, W. J., III; Ryzhkov, L.; Taggi, A. E.; Lectka, T. *J. Am. Chem. Soc.* **2002**, *124*, 67−77.

TABLE 12. Cycloisomerization to Benzofuran Derivatives[b]

entry	substrate	product	yield (%)
1	 **18a**	 **19a**	78
2	 **18b**	 **19b**	76
3	 **18c**	 **19c**	73
4	 **18d**		27[a]

[a] 62% of **18d** was recovered. [b] Conditions: **B** (10 mol %), **6a** (1 equiv) toluene, 2 h, reflux.

TABLE 13. Cycloisomerization of Dienes[a]

entry	substrate	product (yield, %)	recovery (%)
1	 **1r**	 **3r** (26)  **5r** (58)	
2	 **1s**	 **3s** (32)	**1s** (57)
3	 **3s**	 **5s** (66)	**3s** (21)
4	 **1t**	 **3t** (34)  **5t** (52)	
5	 **3t**	**5t** (80)	**3t** (20)

[a] Conditions: **B** (10 mol %), **6a** (1 equiv), xylene, reflux, 2 h.

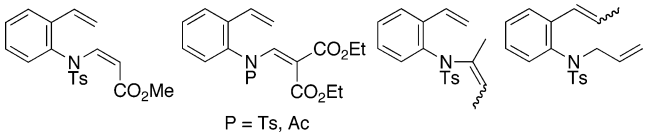


FIGURE 2. Dienes which could not give cycloisomerization product.

ditions using Schlenck technique.[9l] However, strong support for our working hypothesis obtained from the reaction performed in a glovebox, which kept the oxygen and moisture concentrations below 1 ppm. We finally found that the reaction of **B** with **6a** gave ruthenium hydride **E** in quantitative yield (Scheme 4). Although this catalyst was easily decomposed under aerobic conditions, it could be stored without any decomposition if kept in a glovebox. There are only two reports concerning the synthesis of **E** and nobody reports chemical activities of **E**. Grubbs and co-workers reported that **E** is generated by the partial decomposition of **B** in MeOH.[12] Mol and co-workers reported the preparation of **E** from another ruthenium hydride (RuClH-(CO)(PCy_3)$_2$).[13] However, neither methods could give **E** 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 **E** can efficiently catalyze the isomerization of terminal olefins and the cycloisomerization of dienes.

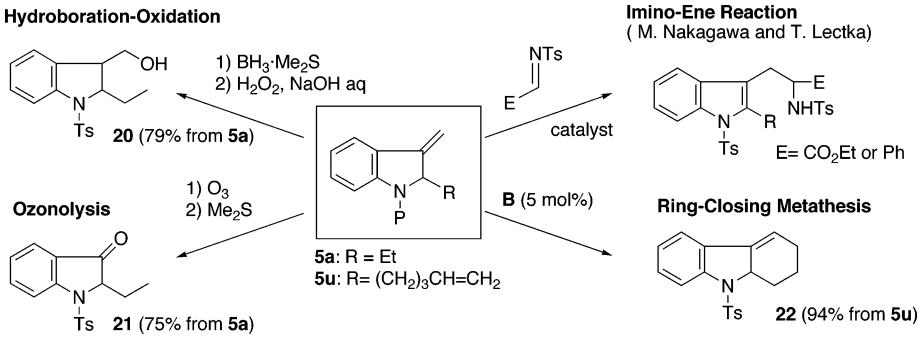
When **B** was reacted with **6f** in toluene (0.01 M) at 50 °C for 1 h, Fischer carbene catalyst **F** was obtained quantitatively, as reported by Grubbs.[14] Heating of **F** in toluene at 110 °C gave **E** quantitatively. The presence of excess **6f** did not affect the conversion of **F** to **E**. At the same time, **F** has RCM activity[14] but does not have isomerization or cycloisomerization

(12) Trnka, T. M.; Morgan, J. P.; Sanford, M. S.; Wilhelm, T. E.; Scholl, M.; Choi, T.-L.; Ding, S.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 2546−2558.

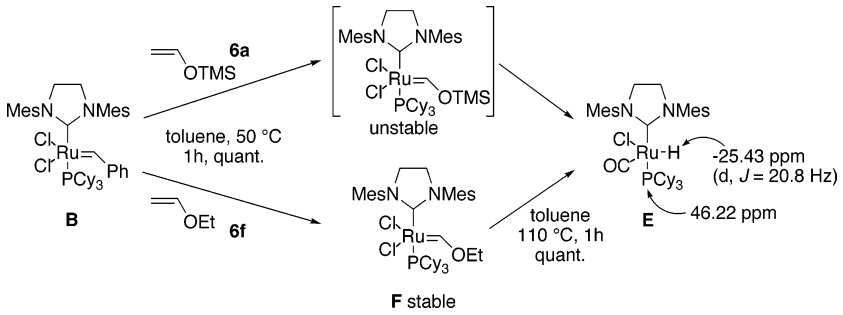
(13) Dinger, M. B.; Mol, J. C. *Eur. J. Inorg. Chem.* **2003**, 2827−2833.

(14) Louie, J.; Grubbs, R. H. *Organometallics* **2002**, *21*, 2153−2164.

SCHEME 3. Reactions of the 3-Methylene Group



SCHEME 4. Quantitative Conversion of B to E



activity. Therefore, in our reaction system (selective isomerization of terminal olefin and cycloisomerization of α,ω-diene), **6f** interferes with **B** from reacting with terminal olefin or diene and efficiently converts **B** to **E** through **F**. We found strong evidence for the generation of RuH complex (**E**) in pure form.

Conclusion

We found that a ruthenium hydride complex (**E**) with an *N*-heterocyclic carbene ligand is generated in pure form by the reaction of **B** with **6a**. Complex **E** showed high catalytic activity in the selective isomerization of terminal olefin and the cycloisomerization of diene. Substituted 1,2-dihydroquinoline (**2**), indole (**4**), and 3-methylene-2,3-dihydroindole (**5**) were prepared selectively from the common starting material **1** and catalyst **B** by slight modification of the reaction conditions (Scheme 1). These procedures address an important issue in diversity-oriented synthesis.[15] The cycloisomerization of *N*-allyl-*o*-vinylaniline efficiently gave 2,3-disubstituted indole, which should be an important synthon for biologically active natural products.

The total synthesis of biologically active natural products with use of the isomerization of terminal olefin or cycloisomerization is currently underway in our laboratory.

Experimental Section

General Procedure for RCM. To a solution of diene was added ruthenium catalyst under an Ar atmosphere. The mixture was stirred as indicated in the tables. After removal of the solvent, the residue was purified by column chromatography on silica gel to give the corresponding cyclized product.

General Procedure for the Isomerization of Terminal Olefin. To a stirred solution of terminal olefin (substrate) and **6a** (1 equiv) in dichloromethane was added ruthenium carbene catalyst (0.05 equiv) under an argon atmosphere and the mixture was refluxed for 1.5−4 h. The solvent was removed under vacuum and the resulting crude residue was subjected to column chromatography to give isomerized product.

General Procedure for Cycloisomerization. To a solution of dieneand **6a** was added ruthenium carbene catalyst **B** (0.10 equivalent) under an Ar atmosphere and the mixture was refluxed for 2 h. The solvent was removed under vacuum and the resulting crude residue was subjected to column chromatography on silica gel to give the corresponding cycloisomerized product.

Acknowledgment. This research was supported by Grants-in-Aid for the Encouragement of Young Scientists (A), for Scientific Research (B), for Priority Area (A) and for Exploratory Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan. We also thank the Naito Foundation and the Fujisawa Foundation for financial support.

Supporting Information Available: Full characterization of compounds **1a**−**e**, **1g**, **1j**−**1t**, **2a**−**c**, **2e**, **2g**, **2j**−**2*l***, **3s**, **3t**, **4a**−**4j**, **4l**−**4q**, **5a**, **5c**−**5e**, **5h**−**5k**, **5m**−**5u**, **8**, **12a**−**12f**, **15**, **16**, **18b, 18c**, **19a**−**19c**, **20**, **21**, and **22**, and catalysts **E** and **F**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO060308U

(15) Burke, M. D.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 46−58.