CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.200801439

Acceleration Effect of an Allylic Hydroxy Group on Ring-Closing Enyne Metathesis of Terminal Alkynes: Scope, Application, and Mechanistic Insights

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Abstract: An interesting acceleration effect of an allylic hydroxy group on ring-closing enyne metathesis has been found. Ring-closing enyne metathesis of terminal alkynes possessing an allylic hydroxy group proceeded smoothly without the ethylene atmosphere generally necessary to promote the reaction. The synthesis of (+)-isofagomine with the aid of this efficient reaction has been demonstrated. Mechanistic studies of the acceleration effect were also carried out. Results of NMR studies suggested that the reaction proceeded via an "ene-then-yne" pathway. Kinetic studies indicated switching of the rate-determining step as a consequence of the presence of an allylic hydroxy group. These results suggest acceleration of the reentry step of Ru-carbene species by the allylic hydroxy group.

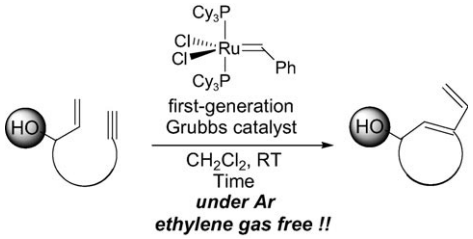
Keywords: (+)-isofagomine · kinetics · reaction mechanisms · ring-closing enyne metathesis · substituent effects

Introduction

Metathesis catalyzed by Ru–alkylidene catalysts has emerged as a powerful synthetic method.[1] The inherent characteristic properties of Ru–alkylidene catalysts—particularly their remarkable functional group compatibility, air- and moisture-insensitivity, and thermal stability, even in toluene at reflux—expand the utility of metathesis. The reaction has contributed greatly to organic synthesis.[2] Despite its popularity, however, our knowledge of the interplay of structure and efficiency in metathesis is limited. Substituents on a substrate often activate or deactivate the substrate and greatly affect reactivity and/or selectivity in metathesis, although not usually in a readily controllable manner.[3–8] Better fundamental understanding and application of those substituent effects are important for the execution of efficient and selective molecular transformations. Extensive works have been devoted to study of the substituent effects of metathesis.[3–8]

In particular, the presence of a hydroxy group often shows interesting effects.[4,6–8] Hoye and Zhao found an acceleration effect of an allylic hydroxy group in ring-closing olefin metathesis with the first-generation Grubbs catalyst.[4a–c] Modulation of the ring size of a ring-closing olefin metathesis by the activation effects of an allylic hydroxy group has also been demonstrated.[4d,e,5] On the other hand, there are several reported instances of negative effects of an allylic hydroxy group decreasing the efficiency of olefin metathesis.[6,7] A few reports of substituent effects of a hydroxy group in enyne metathesis have also been reported.[8,9] We have reported an acceleration effect of an allylic hydroxy group in ring-closing enyne metathesis (Scheme 1).[8a] Very recently, Diver and co-workers also reported an acceleration effect of an allylic hydroxy group in cross-metathesis.[8b]

In this report we give details of a study of the acceleration effect of an allylic hydroxy group on ring-closing enyne



Scheme 1. Allylic hydroxy group-accelerated enyne metathesis.[8a]

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.200801439.

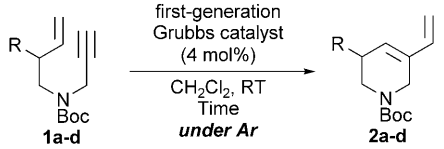
metathesis. In general, ring-closing enyne metathesis of terminal alkynes in the presence of the first-generation Grubbs catalyst is known to be a slow reaction. An ethylene atmosphere is necessary to promote the reaction efficiently.[10] On the other hand, the ring-closing enyne metathesis of enyne substrates possessing an allylic hydroxy group proceeded smoothly in the absence of an ethylene atmosphere (under Ar). The substrate scope of this acceleration effect of an allylic hydroxy group and the effects of hydroxy groups at other positions were investigated. As an application of the efficient reaction based on the acceleration effect of an allylic hydroxy group, a synthesis of (+)-isofagomine was accomplished.

Mechanistic studies of substituent effects on metathesis are relatively rare.[3h,11] Improved knowledge of mechanisms should lead to extended application of substituent effects and the design of new reactions. Mechanistic insights into the acceleration effect are also described.

Results and Discussion

Ring-closing enyne metathesis is a powerful tool for construction of carbo- and heterocyclic compounds.[1c,d] In conjunction with our ongoing studies on aza-sugars,[12] we investigated enyne metathesis of *N*-containing enyne substrates for the construction of 1,2,5,6-tetrahydropyridine frameworks. During these studies, we identified an interesting substituent effect on ring-closing enyne metathesis. N-Containing enyne substrates (**1a**–**d**) were treated with the first-generation Grubbs catalyst (4 mol%) in CH_2Cl_2 at room temperature. The results are summarized in Table 1.

Table 1. Acceleration effect of allylic hydroxy group.



Entry	Substrate	R	Time [h]	Product	Yield[a,b] [%]
1	**1a**	H	41	**2a**	32 (41)
2[c]	**1a**	H	1.5	**2a**	96
3	**1b**	***OH***	***1.5***	**2b**	***>99***
4	**1c**	OBn	41	**2c**	44 (32)
5	**1d**	OTBDPS	41	**2d**	7 (73)

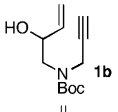
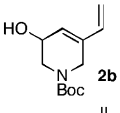
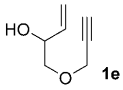
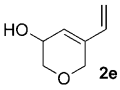
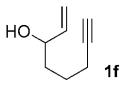
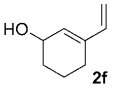
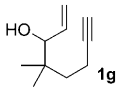
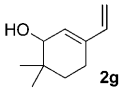
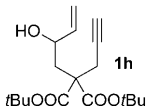
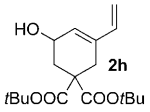
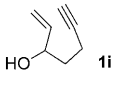
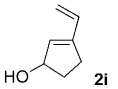
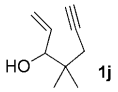
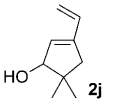
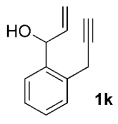
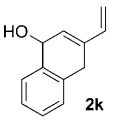
[a] Yield of isolated product. [b] Values in parentheses are yields of recovery estimated from the ^{1}H NMR spectrum of a crude reaction mixture. [c] The reaction was performed under ethylene atmosphere. Boc = *tert*-butoxycarbonyl, Bn = benzyl, TBDPS = *tert*-butyldiphenylsilyl.

An interesting effect of the allylic hydroxy group was highlighted by the results. Enyne metathesis of the substrate *without* an allylic substituent (**1a**) proceeded slowly, and only a 32% yield of product (**2a**) had been obtained after 41 h, with 41% recovery of the starting material (Table 1, entry 1). The efficiency of the reaction is low. On the other hand, the enyne metathesis of the substrate *with* an allylic hydroxy group (**1b**) proceeded rapidly (Table 1, entry 3). After a short time, the reaction had afforded the desired product (**2b**) quantitatively (1.5 h, >99%). This acceleration effect of an allylic hydroxy group is comparable to the acceleration effect of an ethylene atmosphere, which is a known accelerator of ring-closing enyne metathesis of terminal alkynes (Table 1, entry 2).

In addition, the acceleration is specific to an allylic hydroxy group. Protection of the allylic hydroxy group by a Bn or TBDPS group decreased the reaction efficiency (Table 1, entries 4 and 5). These results clearly indicate an acceleration effect of the allylic hydroxy group.

We then investigated the scope of this acceleration effect of an allylic hydroxy group. Ring-closing metathesis of various *N*-, *O*-, and *C*-tethered enynes, each containing an allylic hydroxy group, was investigated in the presence of the first-generation Grubbs catalyst (4 mol%) in CH_2Cl_2 at RT (Table 2). The enyne metathesis of an *O*-tethered enyne

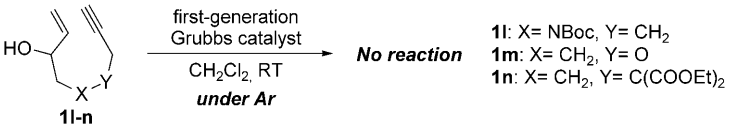
Table 2. Scope of the acceleration effect of an allylic hydroxy group.

Entry	Substrate	Conditions[a]	Time [h]	Product	Yield [%][b,c]
1		A	1.5		>99
2		A	1.5		99
3		A	44.5		74 (17)
4		B	1		66
5		A	32		>99
6		B	5		66
7		A	48.5		76
8		B	3		77
9		A	4		79
10		A	44		15
11		B	16.5		45
12		C	1.5		61
13		A	1		>99[d]

[a] Conditions A: first-generation Grubbs catalyst (4 mol%, 0.002 M), CH_2Cl_2, RT; conditions B: first-generation Grubbs catalyst (8 mol%, 0.002 M), CH_2Cl_2, RT; conditions C: first-generation Grubbs catalyst (12 mol%, 0.002 M), CH_2Cl_2, RT. [b] Yield of isolated product. [c] Values in parentheses are yields of recovery estimated from ^{1}H NMR spectrum of the crude reaction mixture. [d] Since **2k** is easily transformed into 2-vinylnaphthalene, the yield was calculated from the sum of **2k** and 2-vinylnaphthalene (**2k**/2-vinylnaphthalene 74:26). After 14 h, **2k** had been completely converted into 2-vinylnaphthalene.

(**1e**) to form a six-membered cyclic 1,3-diene (**2e**) proceeded with an excellent yield (99%) and in a short time (Table 2, entry 2). *C*-Tethered enynes with and without substituents on the tethered chain (**1f–j**) smoothly promoted ring-closing enyne metathesis to afford five- and six-membered cyclic products (**2f–j**) (Table 2, entries 3–12). Although some reactions took a long time and had low efficiency, almost all of these reactions were complete in short times with higher catalyst loadings, giving cyclic products in good yields. The reaction of a benzene ring-tethered enyne (**1k**) also proceeded smoothly to yield a bicyclic product (**2k**) in an excellent yield (Table 2, entry 13).

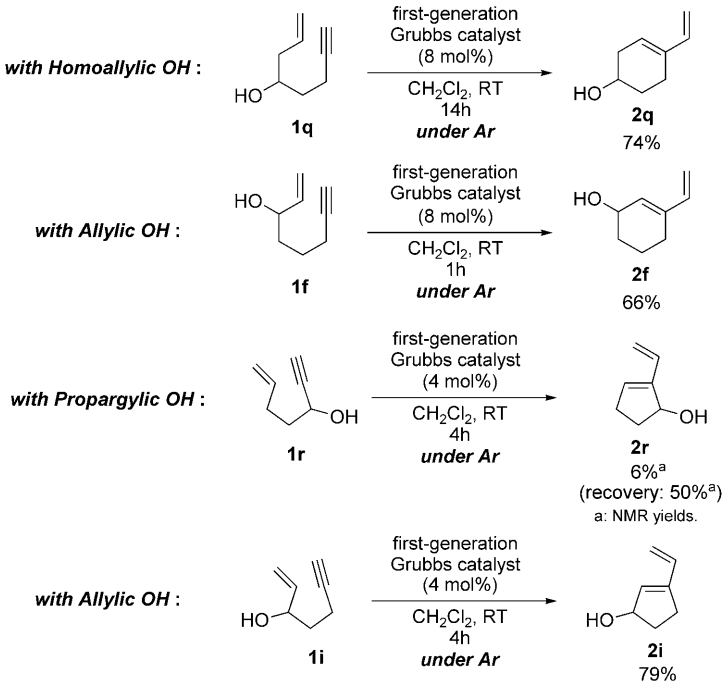
In contrast, no acceleration effect of an allylic hydroxy group was observed in ring-closing enyne metathesis to construct seven-membered ring. No seven-membered ring products were obtained from the corresponding *N*-, *O*-, and *C*-tethered enynes with allylic hydroxy groups (**1l–1n**; Scheme 2). At this point, the reason for this shutdown is unclear.



Scheme 2. Lack of ring-closing enyne metathesis by potential seven-membered ring precursor substrates.

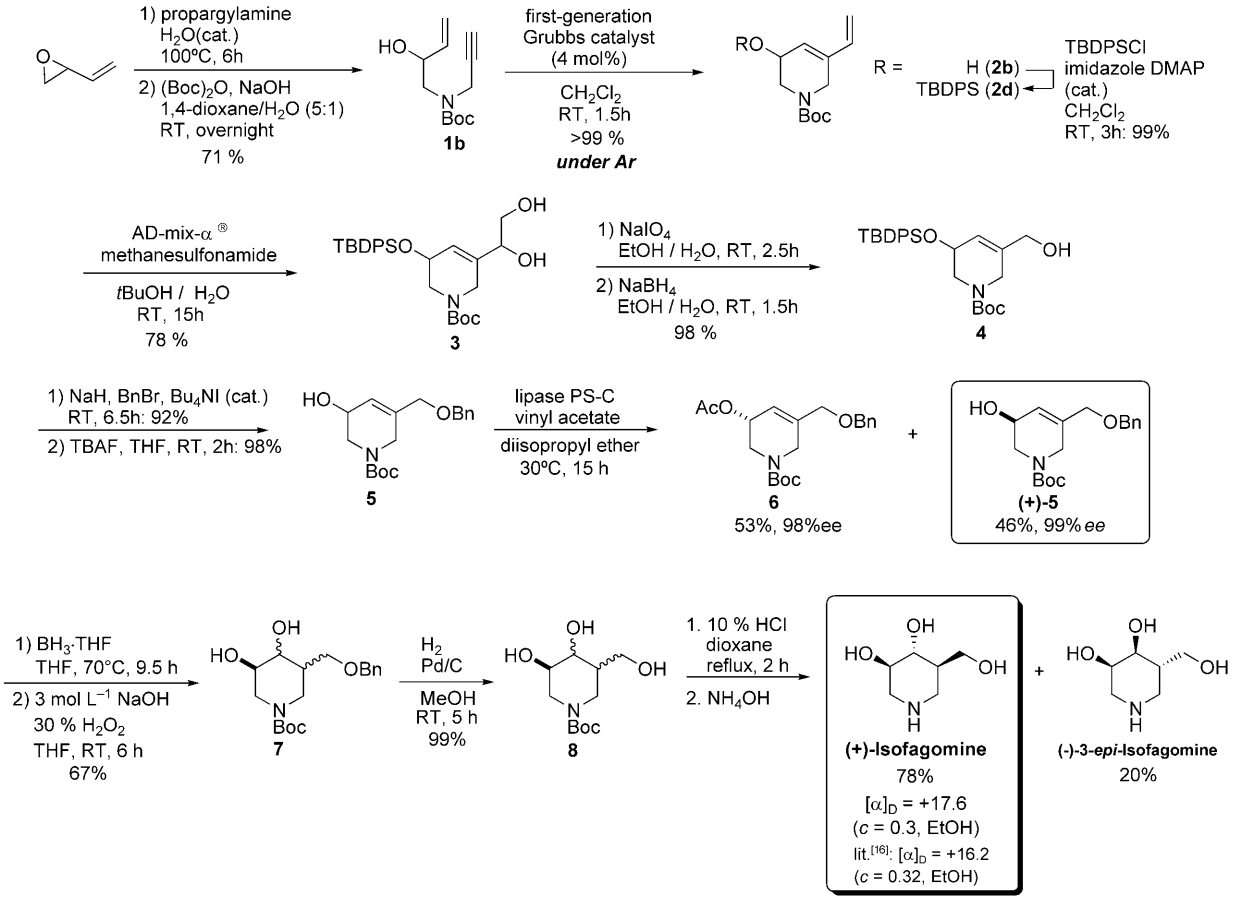
Though there are some limitations, the enyne metathesis of terminal alkynes possessing an allylic hydroxy group proceeds smoothly in the absence of an ethylene atmosphere. The acceleration effect is applicable to a wide range of enyne substrates.

We next investigated the influence of the position of the hydroxy group on the acceleration effect (Scheme 3).[9] We were interested in knowing whether a hydroxy group at another position would also function as an accelerator. A homoallylic hydroxy group showed an acceleration effect weaker than that of an allylic hydroxy group. An enyne substrate with a homoallylic hydroxy group—**1q**—promoted ring-closing enyne metathesis slowly in the presence of the first-generation Grubbs catalyst, although the desired cyclic 1,3-diene (**2q**) was obtained in good yield (74%) after 14 h. The corresponding enyne substrate with an allylic hydroxy group—**1f**—promoted rapid ring-closing enyne metathesis (1 h, 66%) under the same conditions. The effect of a propargylic hydroxy group was also investigated. An enyne substrate with a propargylic hydroxy group—**1r**—showed poor reactivity for ring-closing enyne metathesis. The reaction of **1r** under the same conditions as used for the reaction of **1i** (corresponding enyne substrate with an allylic hydroxy group; first-generation Grubbs catalyst, 4 mol%, RT, 4 h, 79%) provided only a 6% yield of the ring-closure product with 50% recovery of the starting material (NMR yields). These results indicated that an allylic hydroxy group has a strong acceleration effect.



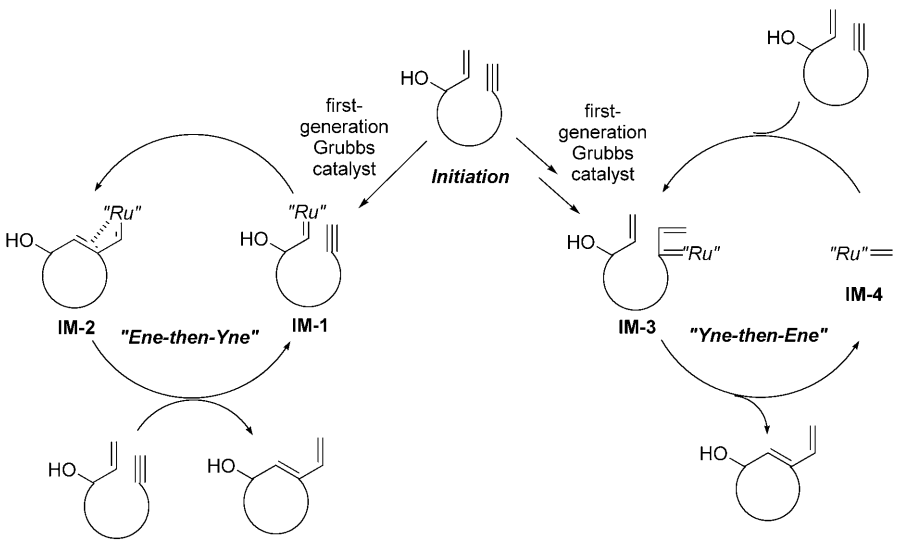
Scheme 3. Influence of position of the hydroxy group.

In a utilization of this efficient ring-closing enyne metathesis based on the acceleration effect of an allylic hydroxy group, a synthesis of (+)-isofagomine was demonstrated (Scheme 4). (+)-Isofagomine is a potent selective β-glucosidase inhibitor that has recently received much attention in Gaucher's disease therapy.[13] The enyne substrate **1b**, with an allylic hydroxy group, was synthesized by addition of propargylamine to butadiene monoxide, followed by protection of the imino group with a Boc group (71% over two steps). The allylic hydroxy group-accelerated ring-closing enyne metathesis of **1b** efficiently provided cyclic product **2b** (>99%) in a short reaction time. The hydroxy group of **2b** was then protected with a TBDPS group (99%), and the TBDPS-protected product **2d** was treated with AD-mix-α.® Highly regioselective dihydroxylation of terminal olefin proceeded to provide diol **3** (78%). Oxidative cleavage of the diol **3** with $NaIO_4$, followed by reduction with $NaBH_4$, gave allyl alcohol **4** (98% over two steps), and protection of the hydroxy group of **4** with a benzyl group (92%) and subsequent removal of the TBDPS group (98%) then provided benzylated product **5**. Kinetic transesterification of **5** with vinyl acetate in the presence of lipase PS-C accomplished excellent resolution of enantiomers, and almost enantiomerically pure (+)-**5** was obtained (46%, 99% *ee*). Hydroboration of the internal olefin of (+)-**5**, followed by oxidation with $NaOH/H_2O_2$, afforded diols **7** (67% over two steps). After removal of both the benzyl group (99%) and the Boc group, (+)-isofagomine (78%) and (−)-3-*epi*-isofagomine (20%) were obtained. (+)-Isofagomine was thus synthesized in an 11.5% total yield from commercially available buta-1,3-diene monoxide.[14,15]



Scheme 4. Application to a synthesis of (+)-isofagomine: DMAP = 4-*N*,*N*-dimethylaminopyridine.

The acceleration effect of an allylic hydroxy group on ring-closing enyne metathesis is interesting. A similar acceleration effect of an allylic hydroxy group has been observed in olefin metathesis in the presence of the first-generation Grubbs catalyst, though details are not clear.[4] To examine the acceleration effect further, we investigated the mechanism of the allylic hydroxy group-accelerated enyne metathesis. We first checked the course of the reaction: "ene-then-yne" or "yne-then-ene" (Scheme 5).[17] ^{1}H NMR analysis of the enyne metathesis of oct-1-en-7-yn-3-ol (**1f**) in the presence of the first-generation Grubbs catalyst (Table 2, entry 3) showed new two signals around 19 ppm, which are attributed to Ru-carbene species (Figure 1, a).[17a,18] Through comparison with related Ru-carbene species generated by straightforward routes (Figure 1, b and c), the two signals are assigned as Ru-(α-hydroxy)carbene species (**IM-1**, 18.92 ppm; Scheme 5) and Ru-vinylcarbene species (**IM-2**, 19.53 ppm), respectively. While these observations do not rule out the possibility of the "yne-then-ene" pathway, they



Scheme 5. Reaction pathways: "ene-then-yne" or "yne-then-ene".

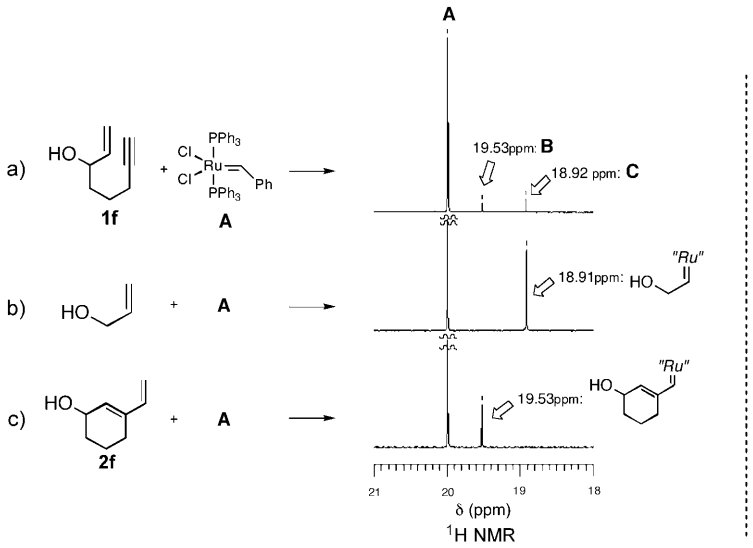


Figure 1. NMR study: "ene-then-yne" versus "yne-then-ene".

provide direct evidence that the "ene-then-yne" pathway is viable. In addition, styrene was detected quickly in the ^{1}H NMR spectrum of the reaction mixture. This observation is further suggestive of initial generation of Ru-(α-hydroxy)-carbene species (**IM-1**).

Selecting the "ene-then-yne" pathway, we speculated that the reentry step of the Ru-carbene species (**IM-1**) from the Ru-vinylcarbene intermediate (**IM-2**; Scheme 5, "ene-then-yne" pathway, **IM-2** to **IM-1**) would be accelerated by an allylic hydroxy group on the next substrate (Scheme 6). The rate-determining step of ring-closing enyne metathesis of a terminal alkyne is thought to be the reentry step (Scheme 5, **IM-2** to **IM-1**).[10,17b,c,19] The reaction rate would be increased if the rate-determining step is accelerated.

On the basis of this speculation, we predicted *switching of the rate-determining step*. If the reentry step of Ru–carbene species (Scheme 5, **IM-2** to **IM-1**) is accelerated by the allylic hydroxy group, the rate-determining step might be replaced by another step of the catalytic cycle because the reentry step would be *faster*. In such cases, a different step of the catalytic cycle would be the rate-determining step rather than the reentry step. Kinetic study of the ring-closing enyne metathesis[11a,b] was carried out to confirm the change of the rate-determining step. We first investigated the reaction behavior of **1a**, an enyne substrate *without* an allylic hydroxy group, to check the usual rate-determining step of ring-closing enyne metathesis (Figure 2). Generally, the rate-determining step of ring-closing enyne metathesis is believed to be the reentry step of the Ru-carbene species (Scheme 5, **IM-2** to **IM-1**).[10,17b,c,19] The results of a kinetic study of **1a** support the general assumption. Ring-closing enyne metathesis of an enyne substrate without an allylic hydroxy group indicated nearly first-order initial rate dependency on concentration of the substrate. This result indicates involvement of a substrate in the rate-determining step, so the reentry step of the Ru-carbene species (Scheme 5, **IM-2** to **IM-1**) seems to be the rate-determining step.

A kinetic study of ring-closing enyne metathesis of a substrate *with* an allylic hydroxy group, on the other hand, showed different results. Because the reaction of **1b** is too fast for kinetic study to be carried out, we chose **1j** as the substrate for the kinetic study (Figure 3). The kinetic study indicated no initial rate dependency on concentration of the enyne substrate (zero order in enyne substrate). This result means that the enyne substrate is not associated with the rate-

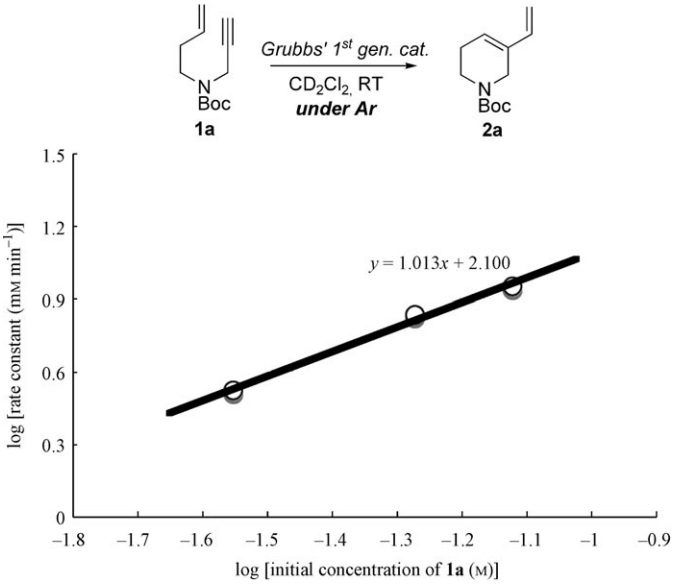


Figure 2. Kinetic study: rate dependency on concentration of a substrate without an allylic hydroxy group.

determining step. From this result, the reentry step of the Ru–carbene species (Scheme 5, **IM-2** to **IM-1**), which involves an enyne substrate, would not be the rate-determining step.

The results of kinetic studies thus indicate a change in the rate-determining step of ring-closing enyne metathesis resulting from the presence or absence of an allylic hydroxy group. These results are consistent with our speculation that the reentry step of the Ru–carbene species from a Ru–vinylcarbene intermediate would be accelerated by the allylic hydroxy group on the next substrate (Scheme 6).[20] In addition, switching of the rate-determining step by an allylic hydroxy group demonstrates that ethylene is not necessary in

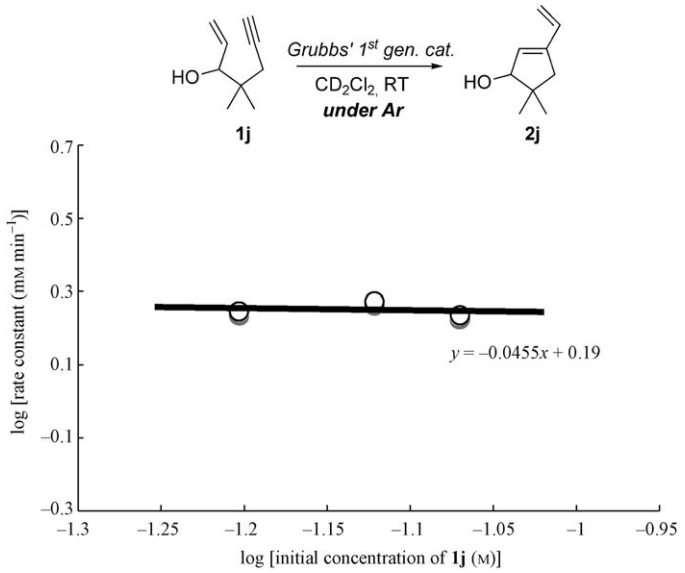
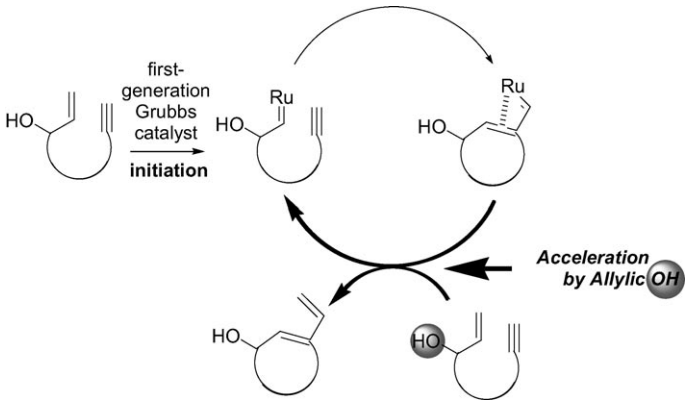


Figure 3. Kinetic study: rate dependence on concentration of a substrate with an allylic hydroxy group.



Scheme 6. Proposed acceleration effect of an allylic hydroxy group.

ring-closing enyne metathesis in the presence of an allylic hydroxy group.[17b,c]

Conclusion

We have found an interesting acceleration effect of an allylic hydroxy group on ring-closing enyne metathesis.[21] The ring-closing enyne metathesis of various terminal alkynes, each containing an allylic hydroxy group, proceeded smoothly in the absence of an ethylene atmosphere. The ethylene-free reaction is convenient and atom-economical. In addition, the metatheses with the first-generation Grubbs catalyst often demonstrate more chemoselective transformation than the more reactive newer-generation Ru–carbene catalysts.[22] We believe that enyne metathesis utilizing this acceleration effect could be a more helpful and familiar tool in organic synthesis. Indeed, we have accomplished the synthesis of (+)-isofagomine with the aid of allylic hydroxy group-accelerated ring-closing enyne metathesis. Mechanistic studies on the acceleration effect have suggested acceleration of the reentry step of Ru–carbene species from the Ru–vinylcarbene species in the catalytic cycle (Scheme 6). The olefin with an allylic hydroxy group on the substrate would be reactive enough to react with the stable Ru–vinylcarbene intermediate to bring about the reentry of the reactive Ru-carbene species into next catalytic cycle. However, details of the acceleration, especially why the acceleration occurs, are still unclear.[23] Further investigations into the mechanism of the acceleration are currently underway. In addition, application of this acceleration effect to other systems and the development of selective molecular transformations using this acceleration effect are proceeding in our laboratory.

Experimental Section

General: NMR spectra were recorded on JNM-EX270 (270 MHz), JEOL JNM-AL400 (400 MHz), JNM-EX400 (400 MHz), and JNM-EX600 (600 MHz) spectrometers in $CDCl_3$, C_6D_6, D_2O, and CD_2Cl_2. ^{13}C NMR spectra were recorded with use of broad-band proton decoupling. The residual $CHCl_3$ signal or tetramethylsilane were used as internal standards for ^1H and ^{13}C NMR in $CDCl_3$. The C_6D_6 itself was used as an internal standard for ^{13}C NMR in C_6D_6. The residual non-deuterated H_2O signal was used as an internal standard for ^1H NMR, and acetonitrile was used as an internal standard in ^{13}C NMR in D_2O. CD_2Cl_2 was used in NMR studies and ^1H NMR spectroscopic kinetic studies. In NMR studies, the chemical shift of the residual non-deuterated CH_2Cl_2 was used as an internal standard. In kinetic studies, CH_2ClCH_2Cl was used as internal standard both for chemical shift and for concentration. Chemical shifts are expressed in δ (ppm) values, and coupling constants are expressed in hertz (Hz). The following abbreviations are used: s = singlet, d = doublet, m = multiplet, br s = broad singlet, br d = broad doublet, dd = double doublet, and ddd = double double doublet. Mass spectra were recorded on JEOL JMN-DX303 or JEOL JMA-DA5000 spectrometers. IR spectra were measured with a Perkin–Elmer 1725 X series FT-IR spectrometer. CH_2Cl_2 was bubbled with Ar well before use in ring-closing enyne metathesis.

General procedure for allylic hydroxy group-accelerated ring-closing enyne metathesis: The first-generation Grubbs catalyst (4, 8, or 12 mol %) was added at room temperature under Ar to a CH_2Cl_2 solution of an enyne substrate[24] containing an allylic hydroxy group. The concentration of the first-generation Grubbs catalyst was kept at 0.002 M. The mixture was stirred for the indicated reaction time. The reaction mixture was then concentrated in vacuo, and the residue was purified by silica gel column chromatography to provide a cyclic 1,3-diene.

***N-tert*-Butoxycarbonyl-3-vinyl-1,2,5,6-tetrahydropyridine (2a)**: ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.47$ (s, 9H), 2.22 (s, 2H), 3.48 (t, $J = 5.6$ Hz, 2H), 4.04 (s, 2H), 4.97 (d, $J = 11.1$ Hz, 1H), 5.07 (d, $J = 17.9$ Hz, 1H), 5.84 (s, 1H), 6.30 ppm (dd, $J = 17.9$, 11.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 25.4$, 27.4, 28.4, 39.6, 40.8, 42.3, 42.8, 79.6, 85.1, 111.0, 126.7, 127.4, 133.4, 136.9, 146.7, 154.9 ppm; IR (neat): $\tilde{\nu} = 1697$ cm^{-1}; EI-MS: m/z: 209 $[M]^+$; HRMS: m/z: calcd for $C_{12}H_{19}NO_2$: 209.1416; found: 209.1424.

***N-tert*-Butoxycarbonyl-5-hydroxy-3-vinyl-1,2,5,6-tetrahydropyridine (2b)**: ^1H NMR (600 MHz, $CDCl_3$, TMS): $\delta = 1.48$ (s, 9H), 2.23 (s, 2H), 3.55 (br s, 2H), 3.95 (d, $J = 17.6$ Hz, 1H), 4.10–4.26 (m, 2H), 5.12 (d, $J = 11.0$ Hz, 1H), 5.22–5.25 (m, 1H), 5.87 (br s, 1H), 6.30 ppm (dd, $J = 17.6$, 11.0 Hz, 1H); ^{13}C NMR (67.5 MHz, C_6D_6, 60 °C): $\delta = 28.5$, 43.0, 48.2, 64.2, 79.8, 113.1, 130.3, 135.7, 136.7, 155.1 ppm; IR (neat): $\tilde{\nu} = 1683$, 3406 cm^{-1}; EI-MS: m/z: 225 $[M]^+$; HRMS: m/z: calcd for $C_{12}H_{19}NO_3$: 225.1365; found: 225.1370.

***N-tert*-Butoxycarbonyl-5-benzyloxy-3-vinyl-1,2,5,6-tetrahydropyridine (2c)**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.48 (s, 9H), 3.48–3.85 (m, 2H), 4.06 (d, J = 15.0 Hz, 3H), 4.58 (d, J = 11.6 Hz, 1H), 4.66–4.68 (m, 1H), 5.10 (d, J = 11.1 Hz, 1H), 5.14–5.31 (m, 1H), 5.89 (s, 1H), 6.31 ppm (dd, J = 17.9, 11.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.4, 42.9, 44.8, 70.4, 70.6, 80.0, 113.4, 113.9, 126.5, 127.7, 128.4, 136.0, 136.1, 138.2, 154.8 ppm; IR (neat): $\tilde{\nu}$ = 1696 cm^{-1}; EI-MS: m/z: 315 $[M]^+$; HRMS: m/z: calcd for $C_{19}H_{25}NO_3$: 315.1834; found: 315.1829.

***N-tert*-Butoxycarbonyl-5-*tert*-butyldiphenylsilyloxy-3-vinyl-1,2,5,6-tetrahydropyridine (2d)**: ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 1.00 (s, 9H), 1.33 (s, 9H), 3.13 (dd, J = 12.4, 6.8 Hz, 1H), 3.58–3.61 (m, 1H), 3.82 (d, J = 16.6 Hz, 1H), 4.04 (d, J = 17.1 Hz, 1H), 4.24 (brs, 1H), 4.96 (d, J = 11.2 Hz, 1H), 5.08 (d, J = 17.6 Hz, 1H), 5.56 (brs, 1H), 6.13 (dd, J = 17.8, 11.0 Hz, 1H), 7.28–7.38 (m, 6H), 7.59–7.63 ppm (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.2, 26.9, 28.4, 42.0, 48.0, 65.5, 79.8, 127.6, 127.6, 127.7, 129.7, 129.8, 135.5, 135.7, 135.8, 154.7 ppm; IR (neat): $\tilde{\nu}$ = 1699 cm^{-1}; EI-MS: m/z: 463 $[M]^+$; HRMS: m/z: calcd for $C_{28}H_{37}NO_3Si$: 463.2543; found: 463.2522.

5-Vinyl-3,6-dihydro-2*H*-pyran-3-ol (2e): Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.04 (brs, 1H), 3.70 (dd, J = 11.6, 2.9 Hz, 1H), 3.85 (dd, J = 11.6, 1.9 Hz, 1H), 4.04 (brs, 1H), 4.18 (d, J = 15.9 Hz, 1H), 4.38 (d, J = 15.5 Hz, 1H), 5.09 (d, J = 18.4 Hz, 1H), 5.10 (d, J = 10.6 Hz, 1H), 5.93 (d, J = 5.9 Hz, 1H), 6.25 ppm (dd, J = 18.4, 11.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 63.0, 65.1, 70.8, 114.0, 126.3, 135.3, 137.9 ppm; IR (neat): $\tilde{\nu}$ = 1007, 1123, 1606, 1648, 2849, 3390 cm^{-1}; EI-MS: m/z: 126 $[M]^+$; HRMS: m/z: calcd for $C_7H_{10}NO_2$: 126.0681; found: 126.0676.

3-Vinylcyclohex-2-en-1-ol (2f): Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.56–1.64 (m, 2H), 1.71 (brs, 1H), 1.79–1.90 (m, 2H), 2.11–2.15 (m, 2H), 4.29 (brs, 1H), 5.04 (d, J = 10.7 Hz, 1H), 5.20 (d, J = 17.6 Hz, 1H), 5.75 (brs, 1H), 6.34 ppm (dd, J = 17.6, 10.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.8, 23.7, 32.0, 66.2, 112.9, 130.8, 138.6, 139.2 ppm; IR (neat): $\tilde{\nu}$ = 909, 991, 1049, 1607, 2863, 2935, 3308 cm^{-1}; EI-MS: m/z: 124 $[M]^+$; HRMS: m/z: calcd for $C_8H_{12}O$: 124.0888; found: 124.0889.

6,6-Dimethyl-3-vinylcyclohex-2-en-1-ol (2g): Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.90 (s, 3H), 0.97 (s, 3H), 1.42–1.47 (m, 2H), 1.56–1.62 (m, 1H), 2.10–2.17 (m, 1H), 3.86 (brs, 1H), 5.03 (d, J = 10.6 Hz, 1H), 5.18 (d, J = 17.9 Hz, 1H), 5.65 (brs, 1H), 6.35 ppm (dd, J = 17.9, 11.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.9, 21.5, 26.4, 32.7, 33.9, 74.6, 112.7, 130.5, 137.4, 138.9 ppm; IR (neat): $\tilde{\nu}$ = 990, 1029, 1606, 2920, 3369 cm^{-1}; EI-MS: m/z: 152 $[M]^+$; HRMS: m/z: calcd for $C_{10}H_{16}O$: 152.1201; found: 152.1197.

Di-*tert*-butyl 5-hydroxy-3-vinylcyclohex-3-ene-1,1-dicarboxylate (2h): Colorless, viscous oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.42 (s, 9H), 1.46 (s, 9H), 2.20–2.28 (m, 2H), 2.53 (d, J = 16.9 Hz, 1H), 2.68 (d, J = 16.9 Hz, 1H), 3.07 (d, J = 9.2 Hz, 1H), 4.31 (brs, 1H), 5.10 (d, J = 10.6, 1H), 5.30 (d, J = 17.9 Hz, 1H), 5.76 (brs, 1H), 6.53 ppm (dd, J = 17.4, 11.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.7, 27.8, 29.3, 36.6, 53.8, 64.2, 81.7, 82.1, 113.5, 130.1, 134.4, 138.4, 170.3 ppm; IR (neat): $\tilde{\nu}$ = 1147, 1257, 1369, 1608, 1716, 1729, 2934, 2978, 3522 cm^{-1}; EI-MS: m/z: 324 $[M]^+$; HRMS: m/z: calcd for $C_{18}H_{28}O_5$: 324.1937; found: 324.1947.

3-Vinylcyclopent-2-en-1-ol (2i): Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.72–1.78 (m, 1H), 1.86 (brs, 1H), 2.29–2.39 (m, 2H), 2.55–2.70 (m, 1H), 4.89 (brd, J = 5.3 Hz, 1H), 5.17 (d, J = 11.1 Hz, 1H), 5.21 (d, J = 18.8 Hz, 1H), 5.75 (s, 1H), 6.56 ppm (dd, J = 17.9, 10.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.94, 33.43, 77.31, 116.70, 131.92, 133.08, 145.80 ppm; IR (neat): $\tilde{\nu}$ = 905, 1044, 1591, 2853, 2939, 3339 cm^{-1}; EI-MS: m/z: 110 $[M]^+$; HRMS: m/z: calcd for $C_7H_{10}O$: 110.0732; found: 110.0732.

5,5-Dimethyl-3-vinylcyclopent-2-en-1-ol (2j): Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.08 (s, 3H), 1.09 (s, 3H), 1.32 (brs, 1H), 2.18 (d, J = 15.9 Hz, 1H), 2.36 (d, J = 15.9 Hz, 1H), 4.25 (brs, 1H), 5.15 (d, J = 10.6 Hz, 1H), 5.16 (d, J = 17.4 Hz, 1H), 5.68 (brs, 1H), 6.53 ppm (dd, J = 17.4, 10.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.7, 28.4, 41.7, 44.1, 84.5, 116.4, 131.0, 133.5, 145.0 ppm; IR (neat): $\tilde{\nu}$*favor*993, 1036, 2926, 2956, 3361 cm^{-1}; EI-MS: m/z: 138 $[M]^+$; HRMS: m/z: calcd for $C_9H_{14}O$: 138.1045; found: 138.1047.

3-Vinyl-1,4-dihydronaphthalen-1-ol (2k): This compound is not stable and easily converted into 2-vinylnaphthalene. Compound **2k** was therefore not isolated. ^{1}H NMR data for **2k** were extracted from the ^{1}H NMR spectrum of the mixture of **2k** and 2-vinylnaphthalene. No other characterization data for **2k** could be measured. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.77 (d, J = 9.2 Hz, 1H), 3.47 (dd, J = 21.3, 3.9 Hz, 1H), 3.60 (brd, J = 19.8 Hz, 1H), 5.20 (d, J = 10.6 Hz, 1H), 5.21–5.30 (m, 1H), 5.39 (d, J = 17.4 Hz, 1H), 6.08 (m, 1H), 6.52 (dd, J = 17.4, 10.6 Hz, 1H), 7.24–7.33 (m, 3H), 7.59–7.61 ppm (m, 1H).

2-Vinylnaphthalene: White solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.35 (d, J = 10.6 Hz, 1H), 5.89 (d, J = 17.4 Hz, 1H), 6.90 (dd, J = 17.4, 10.6 Hz, 1H), 7.44–7.50 (m, 2H), 7.65 (dd, J = 8.7, 1.4 Hz, 1H),7.77 (brs, 1H), 7.80–7.85 ppm (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 114.2, 123.2, 125.9, 126.2, 126.4, 127.7, 128.0, 128.1, 133.1, 133.5, 135.0, 136. 9 ppm; IR (KBr): $\tilde{\nu}$ = 3382, 3058, 2933, 1688, 1630, 1600, 1508, 1467,1356, 1284, 1230, 1196, 1125 cm^{-1}; EI-MS: m/z: 154 $[M]^+$; HRMS: m/z: calcd for $C_{12}H_{10}$: 115.0783; found: 115.0779.

Ring-closing enyne metathesis of enynes containing a homoallylic or a propargylic hydroxy group: The reactions were carried out by the General Procedure for allylic hydroxy group-accelerated ring-closing enyne metathesis.

4-Vinylcyclohex-3-enol (2q): ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 1.60–1.75 (m, 2H), 1.89–1.97 (m, 1H), 2.10–2.24 (m, 2H), 2.32–2.38 (m, 1H), 2.48 (brd, J = 17.4 Hz, 1H), 3.97 (m, 1H), 4.94 (d, J = 10.6 Hz, 1H), 5.08 (d, J = 17.4 Hz, 1H), 5.64 (brs, 1H), 6.35 ppm (dd, J = 17.4, 10.6 Hz, 1H); ^{13}C NMR (100 MHz, C_6D_6): δ = 21.9, 30.5, 34.8, 66.9, 110.9, 126.2, 135.6, 139.1 ppm; IR (neat): $\tilde{\nu}$ = 1606, 1644, 3346 cm^{-1}; EI-MS: m/z: 124 $[M]^+$; HRMS: m/z: calcd for $C_{12}H_{19}NO_3$: 124.0888; found: 124.0887.

2-Vinylcyclopent-2-enol (2r): This compound was obtained in quantities too small to isolate and we could not measure spectroscopic data of a pure sample. The ^{1}H NMR data were extracted from a spectrum of a mixed sample with reference to reported data.[25] ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 1.82–1.88 (m, 1H), 2.17–2.35 (m, 2H), 2.54–2.61 (m, 1H), 4.90–5.10 (m, 1H), 5.15 (d, J = 10.6 Hz, 1H), 5.42 (d, J = 17.9 Hz, 1H), 5.89 (t, J = 2.4 Hz, 1H), 6.47 ppm (dd, J = 17.9, 10.6 Hz, 1H). The yield was estimated from the ^{1}H NMR spectrum of the crude reaction mixture based on internal standard.

Application to the synthesis of (+)-isofagomine

***tert*-Butyl 2-hydroxybut-3-enylprop-2-ynylcarbamate (1b)**: Butadiene monoxide (18 mmol) was added at 15 °C to a solution of propargylamine (54 mmol) and H_2O (0.25 mL), and the mixture was stirred at 100 °C for 6 h. The mixture was then concentrated in vacuo, and the residue was dissolved in 1,4-dioxane (25 mL) and H_2O (5 mL). NaOH (1 N, 20 mL, 20 mmol) and Boc_2O (20 mmol) were added to the solution at ambient temperature, and the mixture was stirred overnight. The solvent was evaporated in vacuo, and the residue was diluted with Et_2O. The mixture was washed with aqueous citric acid solution (20%) and brine. The organic layer was dried over Na_2SO_4. The solvent was evaporated in vacuo, and the residue was purified by silica gel column chromatography (*n*-hexane/AcOEt 10:1–6:1) to provide **1b** (2.87 g, 71% yield) and *tert*-butyl 2-hydroxybut-3-enylprop-2-ynylcarbamate (132 mg). Compound **1b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.46 (s, 9H), 2.24 (t, J = 2.4 Hz, 1H), 3.37 (brs, 1H), 3.44 (dd, J = 14.6, 3.8 Hz, 2H), 4.07 (brs, 2H), 4.35–4.39 (m, 1H), 5.16 (d, J = 10.6 Hz, 1H), 5.33 (brd, J = 16.4 Hz, 1H), 5.84 ppm (ddd, J = 16.4, 10.6, 5.8 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.3, 38.3, 52.9, 71.7, 72.2, 79.6, 81.0, 115.9, 138.1, 156.3 ppm; IR (neat): $\tilde{\nu}$ = 1683, 3441 cm^{-1}; EI-MS: m/z: 225 $[M]^+$; HRMS: m/z: calcd for $C_{12}H_{19}NO_3$: 225.1365; found: 225.1361.

1-*tert*-Butoxycarbonyl-3-vinyl-1,2,5,6-tetrahydropyridin-3-ol (2b): Compound **2b** was synthesized by the allylic hydroxy group-accelerated ring-closing enyne metathesis (Table 2, entry 1).

1-*tert*-Butoxycarbonyl-5-*tert*-butyldiphenylsilyloxy-3-vinyl-1,2,5,6-tetrahydropyridine (2d): Imidazole (7.02 mmol), DMAP (0.094 mmol), and TBDPSCl (5.15 mmol) were added at ambient temperature to a solution of **2b** (4.68 mmol) in CH_2Cl_2 (20 mL), and the mixture was stirred for 1 h. The mixture was then filtered with a pad of celite. The filtrate was washed with brine and dried over Na_2SO_4. The solvent was evaporated in

vacuo, and the residue was purified by silica gel column chromatography (*n*-hexane/AcOEt 8:1) to provide **2d** (2141 mg, 99% yield).

1-*tert*-Butoxycarbonyl-5-*tert*-butyldiphenylsilyloxy-3-(1,2-dihydroxyethyl)-1,2,5,6-tetrahydropyridine (3): AD-mix-α and methanesulfonamide (0.30 mmol) were added at ambient temperature to a solution of **2d** (0.30 mmol) in *t*BuOH/H_2O (1:1), and the mixture was stirred for 15 h. The mixture was then diluted with AcOEt and washed with saturated aqueous NH_4Cl and H_2O. The organic layer was dried over Na_2SO_4. The solvent was evaporated in vacuo, and the residue was purified by silica gel column chromatography (*n*-hexane/AcOEt 1:1) to provide **3** (116 mg, 78% yield). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.06$ (s, 9H), 1.41 (brs, 9H), 2.49 (brs, 2H), 3.31–3.93 (m, 6H), 4.06 (brs, 1H), 4.27 (brs, 1H), 5.65 (brs, 1H), 7.35–7.45 (m, 6H), 7.65–7.70 ppm (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 19.2$, 26.9, 28.4, 42.5, 48.1, 65.0, 65.3, 73.4, 80.0, 127.6, 127.7, 127.7, 129.8, 135.7, 135.7, 154.9 ppm; IR (neat): $\tilde{\nu} = 1661$, 3407 cm^{-1}; EI-MS: *m*/*z*: 496 $[M+H]^+$, 497 $[M]^+$; HRMS: *m*/*z*: calcd for $C_{28}H_{39}NO_5Si$: 497.2597; found: 497.2587.

***N*-*tert*-Butoxycarbonyl-5-*tert*-butyldiphenylsilyloxy-3-hydroxymethyl-1,2,5,6-tetrahydropyridine (4)**: $NaIO_4$ (2.04 mmol) was added at ambient temperature to a solution of **3** (1.70 mmol) in EtOH/H_2O (1:1, 30 mL), and the mixture was stirred for 3 h. $NaBH_4$ (3.40 mmol) was then added to the mixture at ambient temperature. After the mixture had been stirred for 3 h, the reaction mixture was concentrated in vacuo, and the residue was diluted with CH_2Cl_2. The mixture was washed with $Na_2S_2O_3$ (10%), saturated aqueous $NaHCO_3$, and brine. The organic layer was dried over Na_2SO_4. The solvent was evaporated in vacuo, and the residue was purified by silica gel column chromatography (*n*-hexane/AcOEt 2:1) to provide **4** (776 mg, 98% yield). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.07$ (s, 9H), 1.39–1.45 (m, 9H), 2.19 (brs, 1H), 3.27 (dd, $J = 12.8$, 6.6 Hz, 1H), 3.59 (d, $J = 9.9$ Hz, 1H), 3.76–3.98 (m, 4H), 4.29 (s, 1H), 5.64 (s, 1H), 7.36–7.45 (m, 6H), 7.67–7.70 ppm (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 19.2$, 26.9, 28.3, 43.0, 48.0, 64.2, 65.1, 80.0, 127.6, 127.7, 128.3, 129.8, 135.7, 135.7, 154.7 ppm; IR (neat): $\tilde{\nu} = 1689$, 3419 cm^{-1}; EI-MS: *m*/*z*: 467 $[M]^+$; HRMS: *m*/*z*: calcd for $C_{27}H_{37}NO_4Si$: 467.2492; found: 467.2491.

3-Benzyloxymethyl-1-*tert*-butoxycarbonyl-1,2,5,6-tetrahydropyridin-5-ol (5): NaH (1.68 mmol) was added at 0°C to a solution of **4** (0.84 mmol) in THF (8.0 mL), and the mixture was stirred for 1 hour. Benzyl bromide (2.52 mmol) and tetrabutylammonium iodide (12 mg) were then added to the mixture at 0°C, and the mixture was stirred for 6.5 h at ambient temperature. The resulting mixture was diluted with Et_2O and was washed with saturated aqueous NH_4Cl, water, and brine. The organic layer was dried over Na_2SO_4. The solvent was evaporated in vacuo, and the residue was purified by silica gel column chromatography (*n*-hexane/AcOEt 10:1) to provide benzylated product (431 mg, 92% yield). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.08$ (s, 9H), 1.41 (brs, 9H), 3.36–3.27 (m, 1H), 3.48–3.96 (m, 5H), 4.28 (brs, 1H), 4.41 (s, 2H), 5.67 (brs, 1H), 7.27–7.49 (m, 11H), 7.67–7.71 ppm (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 19.7$, 26.8, 28.3, 43.3, 47.8, 65.0, 71.3, 72.0, 79.5, 126.3, 127.5, 127.6, 127.7, 128.2, 129.6, 129.7, 135.6, 135.6, 137.8, 154.5 ppm; IR (neat): $\tilde{\nu} = 1701$ cm^{-1}; EI-MS: *m*/*z*: 557 $[M]^+$; HRMS: calcd for $C_{34}H_{43}NO_4Si$: 557.2961; found: 557.2958.

Tetrabutylammonium fluoride (2.1 mmol) was added at room temperature to a solution of the obtained benzylated product (1.7 mmol) in THF (20 mL), and the mixture was stirred at room temperature for 1.5 h. The solvent was then evaporated in vacuo, and the residue was diluted with $CHCl_3$. The mixture was washed with saturated aqueous $NaHCO_3$, and the resulting aqueous phase was extracted with $CHCl_3$. The combined organic extracts were washed with brine and then dried over Na_2SO_4. The solvent was evaporated in vacuo, and the residue was purified by silica gel column chromatography (*n*-hexane/AcOEt 2:1) to provide **5** (535 mg, 98% yield). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.47$ (s, 9H), 1.80 (s, 1H), 3.52 (brs, 2H), 3.81 (d, $J = 18.4$ Hz, 1H), 3.97–4.11 (s, 3H), 4.21 (brs, 1H), 4.50 (s, 2H), 5.90–5.91 (s, 1H), 7.26–7.39 ppm (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 28.3$, 44.1, 47.2, 63.5, 71.5, 72.3, 80.2, 127.7, 127.7, 127.9, 128.2, 128.4, 137.8, 155.1 ppm; IR (neat): $\tilde{\nu} = 1695$, 3405 cm^{-1}; EI-MS: *m*/*z*: 319 $[M]^+$; HRMS: *m*/*z*: calcd for $C_{18}H_{25}NO_4$: 319.1784; found: 319.1776.

(−)-*N*-*tert*-Butoxycarbonyl-5-acetoxy-3-(benzyloxy)methyl-3-piperidine (6) and (*S*)-*N*-*tert*-Butoxycarbonyl-5-hydroxy-3-(benzyloxy)methyl-1,2,5,6-tetrahydropyridine: Vinyl acetate (96.8 mmol) and lipase PS-C (628 mg) were added at ambient temperature to a solution of **5** (1.21 mmol) in diisopropyl ether (5.8 mL). The mixture was warmed to 30°C and stirred for 15 h. The mixture was then filtered through a pad of celite. The filtrate was concentrated in vacuo, and the residue was purified by silica gel column chromatography (*n*-hexane/AcOEt 10:1) to provide **6** (179 mg, 46% yield) and (+)-**5** (233 mg, 53% yield).

Compound 6: $[\alpha]_D^{27} = -79.6$ ($c = 1.7$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.47$ (s, 9H), 2.05 (s, 3H), 3.40–3.44 (m, 1H), 3.74–3.86 (m, 2H), 3.98 (s, 2H), 4.19 (brs, 1H), 4.50 (s, 2H), 5.19 (brs, 1H), 5.88 (brs, 1H), 7.27–7.37 ppm (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 21.0$, 28.1, 43.3, 44.8, 65.5, 71.1, 72.4, 79.9, 122.3, 127.6, 128.1, 128.3, 137.6, 154.6, 170.4 ppm; IR (neat): $\tilde{\nu} = 1701$, 1735 cm^{-1}; EI-MS: *m*/*z*: 361 $[M]^+$; HRMS: *m*/*z*: calcd for $C_{20}H_{27}NO_5$: 361.1889; found: 319.1883.

Compound (+)-5: $[\alpha]_D^{27} = +45.6$ ($c = 1.0$ in $CHCl_3$); HPLC (Chiralpak IA, hexane/AcOEt 90:10, 1.5 mL min^{-1}, 254 nm): $t_{minor} = 23.4$ min, $t_{major} = 25.9$ min: 99% *ee*. The absolute configuration of (+)-**5** was determined as (*S*) after conversion into (+)-isofagomine as described below.

The *ee* of **6** was determined after cleavage of the benzyl group to convert it into (−)-**5**. K_2CO_3 (0.06 mmol) was added at ambient temperature to a solution of **6** (0.12 mmol) in dry MeOH (1.5 mL). After stirring for 1 hour, the reaction mixture was diluted with AcOEt and washed with water. The aqueous layer was extracted twice with AcOEt, and the combined organic extract was dried over Na_2SO_4. The solvent was evaporated in vacuo, and the residue was purified by silica gel column chromatography (*n*-hexane/AcOEt 1:1) to provide (−)-**5** (36 mg, 94% yield). $[\alpha]_D^{27} = -43.0$ ($c = 1.1$ in $CHCl_3$). The absolute configuration of (−)-**5** was determined as (*R*) based on (+)-**5**.

5-Benzyloxymethyl-1-*tert*-butoxycarbonylpiperidine-3,4-diol (7): BH_3·THF (1.0 M THF solution, 2.1 mL, 2.1 mmol) was added at 0°C to a solution of (+)-**5** (0.26 mmol) in THF (1.0 mL). The reaction mixture was then warmed to 70°C and stirred for 9.5 h. After the stirring, the mixture was cooled to 0°C. NaOH (3 N, 3.0 mL) and H_2O_2 (30%) were added dropwise to the mixture, which was stirred for 6 h at ambient temperature. Then organic and aqueous layers were separated, and the aqueous layer was extracted five times with $CHCl_3$. The combined organic extracts were washed with brine and then dried over Na_2SO_4. The solvent was evaporated in vacuo, and the residue was purified by silica gel column chromatography (*n*-hexane/AcOEt 1:2) to provide **7** (59 mg, 67% yield). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.44$ (s, 9H), 1.84 (brs, 1H), 2.52 (brs, 2H), 3.37–3.48 (m, 2H), 3.58 (brs, 3H), 3.83 (brs, 1H), 4.11–4.19 (m, 2H), 4.51 (s, 2H), 7.27–7.36 ppm (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 28.3$, 44.1, 44.1, 45.3, 47.6, 64.8, 67.2, 70.1, 71.5, 73.3, 80.2, 127.2, 127.5, 127.7, 127.8, 137.7, 140.3, 154.6, 155.7 ppm; IR (neat): $\tilde{\nu} = 1671$, 3395 cm^{-1}; EI-MS: *m*/*z*: 337 $[M]^+$; HRMS: *m*/*z*: calcd for $C_{18}H_{27}NO_5$: 337.1889; found: 337.1898.

1-*tert*-Butoxycarbonyl-5-(hydroxymethyl)piperidine-3,4-diol (8): MeOH (7 mL) was added under H_2 atmosphere at ambient temperature to a mixture of **7** (0.22 mmol) and Pd/C (30 mg). After stirring for 5 h, the reaction mixture was filtered with a pad of celite. The filtrate was concentrated in vacuo, and the residue was purified by silica gel column chromatography (CH_3Cl:MeOH 10:1) to provide **8** (54 mg, 99% yield). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.42$ (s, 9H), 1.67 (brs, 1H), 2.56 (brs, 2H), 3.34–3.55 (m, 2H), 3.69–3.76 (m, 3H), 3.88–4.16 ppm (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 28.4$, 43.4, 47.7, 61.8, 62.8, 71.4, 75.7, 80.5, 155.0 ppm; IR (neat): $\tilde{\nu} = 1669$, 3383 cm^{-1}; EI-MS: *m*/*z*: 247 $[M]^+$; HRMS: *m*/*z*: calcd for $C_{11}H_{21}NO_5$: 247.1420; found: 247.1416.

5-(hydroxymethyl)piperidine-3,4-diols ((+)-isofagomine and (−)-3-*epi*-isofagomine): HCl (10%, 2.7 mL) was added to a solution of **8** (0.20 mmol) in 1,4-dioxane (0.9 mL), and the mixture was heated to reflux. After stirring for 2 h, the reaction mixture was allowed to cool to ambient temperature. Aqueous NH_4OH solution (28%) was then added to basify the mixture, and the solvent was evaporated in vacuo. The residue was purified by silica gel column chromatography (MeOH/10% NH_4OH 10:1) to afford (+)-isofagomine (23 mg, 78% yield) and (−)-3-*epi*-isofagomine (6 mg, 20%).

(+)-Isofagomine: $[\alpha]_D^{27} = +17.6$ ($c = 0.3$ in EtOH) [lit.:[13] $[\alpha]_D^{27} = +16.3$ ($c = 0.32$ in EtOH)]; ^{1}H NMR (600 MHz, D_2O): $\delta = 1.48$–1.57 (m, 1H), 2.21–2.28 (m, 2H), 2.91–3.00 (m, 2H), 3.13 (t, $J = 9.7$ Hz, 1H), 3.30–3.37 (m, 1H), 3.45 (dd, $J = 11.6$, 6.8 Hz, 1H), 3.64 ppm (dd, $J = 11.6$, 3.4 Hz, 1H); ^{13}C NMR (100 MHz, D_2O, CH_3CN): $\delta = 44.4$, 46.3, 49.3, 60.4, 71.9, 73.6 ppm; IR (neat): $\tilde{\nu} = 3383$ cm^{-1}; EI-MS: m/z: 147 $[M]^+$; HRMS: m/z: calcd for $C_6H_{13}NO_3$: 147.0895; found: 147.0889.

(−)-3-*epi*-Isofagomine: $[\alpha]_D^{28} = -19.3$ ($c = 0.6$ in EtOH); ^{1}H NMR (400 MHz, D_2O): $\delta = 2.05$–2.10 (m, 1H), 2.61 (t, $J = 12.6$ Hz, 1H), 2.89 (d, $J = 13.5$ Hz, 1H), 3.16–3.25 (m, 2H), 3.59–3.65 (m, 2H), 3.72 (dd, $J = 11.6$, 3.4 Hz, 1H), 3.98 ppm (s, 1H); ^{13}C NMR (67.8 MHz, D_2O, CH_3CN): $\delta = 37.8$, 45.0, 48.3, 60.1, 66.2, 68.5 ppm; IR (neat): $\tilde{\nu} = 3345$ cm^{-1}; EI-MS: m/z: 147 $[M]^+$; HRMS: m/z: calcd for $C_6H_{13}NO_3$: 147.0895; found: 147.0894.

Procedure for NMR studies to determine reaction pathway: The first-generation Grubbs catalyst (0.025 mmol) was placed in a NMR tube and the tube was equipped with a rubber stopper. Then the tube was dried in vacuo for 30 min. After drying, the tube was placed under Ar. CD_2Cl_2 was added. An equimolar amount of a substrate (0.025 mmol) was added to the mixture at ambient temperature. ^{1}H NMR spectra of the resulting mixtures were then measured.

Procedure for kinetic studies to confirm the change in rate-determining step:[26] The first-generation Grubbs catalyst was dried in vacuo for 30 min, and an appropriate amount of CD_2Cl_2 was added under Ar to prepare a 0.002 M solution of first-generation Grubbs catalyst in CD_2Cl_2. 1,2-Dichloroethane was added to the solution as an internal standard (ca. 0.034 M). This solution (0.6 mL) was then transferred to a dried NMR tube. Just before ^{1}H NMR measurement, a corresponding amount of enyne substrate (**1a**, **1j**) was added to the NMR tube and the tube was shaken intensively. The ^{1}H NMR spectrum was then measured continuously. The concentration of the desired product (**2a**, **2j**) was estimated by integration with 1,2-dichloroethane as an internal standard. Initial reaction rates were estimated from the approximated curves (first order) of the first 5 minutes under each set of conditions.

Acknowledgements

We are grateful for the financial support provided by a Grant-in-Aid for Scientific Research from the Japan Society for the Promotion of Science (JSPS) (no. 18570012) and the High Technology Research Program of the Ministry of Education, Culture, Sports, Sciences and Technology, Japan.

[1] a) R. H. Grubbs, *Tetrahedron* **2004**, *60*, 7117–7140; b) A. H. Hoveyda, A. R. Zhugralin, *Nature* **2007**, *450*, 243–251; c) S. T. Diver, A. Giessert, *Chem. Rev.* **2004**, *104*, 1317–1382; d) H. Villar, M. Frings, C. Bolm, *Chem. Soc. Rev.* **2007**, *36*, 55–66; e) A. Fürstner, *Angew. Chem.* **2000**, *112*, 3140–3172; *Angew. Chem. Int. Ed.* **2000**, *39*, 3012–3043; f) *Handbook of Metathesis, Vol. 3* (Ed.: R. H. Grubbs), Wiley-VCH, Weinheim, **2003**.

[2] K. C. Nicolaou, P. G. Bulger, D. Sarlah, *Angew. Chem.* **2005**, *117*, 4564–4601; *Angew. Chem. Int. Ed.* **2005**, *44*, 4490–4527.

[3] For selected examples of substituent effects on Ru-carbene-catalyzed metathesis, see: a) T. A. Kirkland, R. H. Grubbs, *J. Org. Chem.* **1997**, *62*, 7310–7318; b) X. Guo, K. Basu, J. A. Cabral, L. A. Paquette, *Org. Lett.* **2003**, *5*, 789–792; c) B. Kang, J. M. Lee, J. Kwak, Y. S. Lee, S. Chang, *J. Org. Chem.* **2004**, *69*, 7661–7664; d) N. A. Sheddan, V. B. Arion, J. Mulzer, *Tetrahedron Lett.* **2006**, *47*, 6689–6693; e) D. L. Wright, L. C. Usher, M. Estrella-Jimenez, *Org. Lett.* **2001**, *3*, 4275–4277; f) S. Randl, N. Lucas, S. J. Connon, S. Blechert, *Adv. Synth. Catal.* **2002**, *344*, 631–633; g) T. Kinoshita, Y. Sato, M. Mori, *Adv. Synth. Catal.* **2002**, *344*, 678–693; h) B. R. Galan, A. J. Giessert, J. B. Keister, S. T. Diver, *J. Am. Chem. Soc.* **2005**, *127*, 5762–5763; i) G. Vassilikogiannakis, L. Margaros, M. Tofi, *Org. Lett.* **2004**, *6*, 205–208; j) F.-D. Boyer, I. Hanna, *Eur. J. Org. Chem.* **2006**, 471–482; k) Y. J. Kim, J. B. Grimm, D. Lee, *Tetrahedron Lett.* **2007**, *48*, 7961–7964.

[4] For acceleration effects of an allylic hydroxy group on Ru–carbene-catalyzed olefin metathesis, see: a) T. R. Hoye, H. Zhao, *Org. Lett.* **1999**, *1*, 1123–1125; b) R. M. Kanada, D. Itoh, M. Nagai, J. Niijima, N. Asai, Y. Mizui, S. Abe, Y. Kotake, *Angew. Chem.* **2007**, *119*, 4428–4433; *Angew. Chem. Int. Ed.* **2007**, *46*, 4350–4355; c) K. P. Kaliappan, N. Kumar, *Tetrahedron* **2005**, *61*, 7461–7469. Modulation of ring size of ring-closing metathesis by allylic hydroxy group substituent effects, see: d) B. Schmidt, S. Nave, *Chem. Commun.* **2006**, 2489–2491; e) B. Schmidt, S. Nave, *Adv. Synth. Catal.* **2007**, *349*, 215–230.

[5] Modulation of ring size of ring-closing metathesis by steric hindrance has also been reported. See; a) K. J. Quinn, A. K. Isaacs, R. A. Arvary, *Org. Lett.* **2004**, *6*, 4143–4145; b) K. J. Quinn, A. K. Isaacs, B. A. DeChristopher, S. C. Szklarz, R. A. Arvary, *Org. Lett.* **2005**, *7*, 1243–1245.

[6] a) M. K. Gurjar, *Tetrahedron Lett.* **2001**, *42*, 3633–3636; b) L. A. Paquette, I. Efremov, *J. Am. Chem. Soc.* **2001**, *123*, 4492–4501; c) T. K. Maishal, D. K. Shinha-Mahapatra, K. Paranjape, A. Sarkar, *Tetrahedron Lett.* **2002**, *43*, 2263–2267; d) L. Ackermann, D. E. Tom, A. Fürstner, *Tetrahedron* **2000**, *56*, 2195–2202.

[7] In reference [4a], it is reported that a decomposition mechanism based on an allylic hydroxy group also exists for secondary allylic alcohols, although the ring-closing metathesis proceeds more rapidly. This decomposition decreased the efficiency of the metathesis. For tertiary allylic alcohols, such decomposition was not observed and the metathesis proceeded rapidly and efficiently.

[8] a) T. Imahori, H. Ojima, H. Tateyama, Y. Mihara, H. Takahata, *Tetrahedron Lett.* **2008**, *49*, 265–268; b) D. A. Clark, J. R. Clark, S. T. Diver, *Org. Lett.* **2008**, *10*, 2055–2058.

[9] For effects of a hydroxy group at other positions on Ru–carbene-catalyzed enyne metathesis, see: a) M. Mori, K. Tonogaki, N. Nishiguchi, *J. Org. Chem.* **2002**, *67*, 224–226; b) J. A. Smulik, S. T. Diver, *Org. Lett.* **2000**, *2*, 2271–2274.

[10] M. Mori, N. Sakakibara, A. Kinoshita, *J. Org. Chem.* **1998**, *63*, 6082–6083.

[11] a) A. J. Giessert, S. T. Diver, *Org. Lett.* **2005**, *7*, 351–354; b) A. C. Tsipis, A. G. Orpen, J. N. Harvey, *Dalton Trans.* **2005**, 2849–2858.

[12] For selected examples, see: a) H. Takahata, Y. Suto, E. Kato, Y. Yoshimura, H. Ouchi, *Adv. Synth. Catal.* **2007**, *349*, 685–693; b) H. Ouchi, Y. Mihara, H. Takahata, *J. Org. Chem.* **2005**, *70*, 5207–5214; c) N. Asano, K. Ikeda, L. Yu, A. Kato, K. Takebayashi, I. Adachi, I. Kato, H. Ouchi, H. Takahata, G. W. J. Feet, *Tetrahedron: Asymmetry* **2005**, *16*, 223–229; d) A. Kato, N. Kato, E. Kano, I. Adachi, K. Ikeda, L. Yu, T. Okamoto, Y. Banba, H. Ouchi, H. Takahata, N. Asano, *J. Med. Chem.* **2005**, *48*, 2036–2044; e) H. Takahata, Y. Banba, H. Ouchi, H. Nemoto, *Org. Lett.* **2003**, *5*, 2527–2529; f) H. Takahata, Y. Banba, H. Ouchi, H. Nemoto, A. Kato, I. Adachi, *J. Org. Chem.* **2003**, *68*, 3603–3607.

[13] X. Z. Zhu, K. A. Sheth, S. Li, H.-H. Chang, J.-Q. Fan, *Angew. Chem.* **2005**, *117*, 7616–7619; *Angew. Chem. Int. Ed.* **2005**, *44*, 7450–7453.

[14] For other examples of (+)-isofagomine syntheses, see: a) H. Ouchi, Y. Mihara, H. Watanabe, H. Takahata, *Tetrahedron Lett.* **2004**, *45*, 7053–7056; b) L. Banfi, G. Guanti, M. Paravidino, R. Riva, *Org. Biomol. Chem.* **2005**, *3*, 1729–1737.

[15] The acetylated product **6** in the kinetic transesterification step also had high enantiopurity (53%, 98% *ee*). This product could be utilized in (−)-isofagomine synthesis.

[16] G. Pamdey, M. Kapur, *Synthesis* **2001**, 1263–1267.

[17] Two pathways of ring-closing enyne metathesis—"ene-then-yne" or "yne-then-ene"—are possible. Some mechanistic and computational studies on ring-closing enyne metathesis support the "ene-then-yne" pathway; see: a) T. R. Hoye, S. M. Donaldson, T. J. Vos, *Org. Lett.* **1999**, *1*, 277–279; b) G. C. Lloyd-Jones, R. G. Margue, J. G. de Vries, *Angew. Chem.* **2005**, *117*, 7608–7613; *Angew. Chem. Int. Ed.* **2005**, *44*, 7442–7447; c) J. J. Lippstreu, B. F. Straub, *J. Am. Chem. Soc.* **2005**, *127*, 7444–7457. The "ene-then-yne" pathway is also proposed

in other reports; see: d) A. Kinoshita, M. Mori, *Synlett*, **1994**, 1020–1022; e) E. Vedrenne, F. Royer, J. Oble, L. E. Kaïm, L. Grimaud, *Synlett*, **2005**, 2379–2381; f) N. Dieltiens, K. Moonen, C. V. Stevens, *Chem. Eur. J.* **2007**, *13*, 203–214.

[18] P. Schwab, R. H. Grubbs, J. W. Ziller, *J. Am. Chem. Soc.* **1996**, *118*, 100–110.

[19] The acceleration effect of an ethylene atmosphere (reference [7b,c]) also suggests that regeneration of reactive Ru–carbene species is the rate-determining step.

[20] We cannot rule out the possibility of acceleration by the allylic hydroxy group in the case of Ru–vinylcarbene intermediate **IM-4**. However, we think that the hydroxy group is too far from the Ru center to interact and it seems unlikely.

[21] For effects of other substituents on the rate of Ru–carbene-catalyzed enyne metathesis see references [3g, 3h, and 11a].

[22] While the Grubbs second-generation catalyst displays significantly enhanced activity and thermal stability relative to the first-generation catalyst, overall selectivity is often compromised by competing olefin isomerization; see: S. S. Kinderman, J. H. van Maarseveen, H. E. Schoemaker, H. Hiemstra, F. P. J. T. Rutjes, *Org. Lett.* **2001**, *3*, 2045–2048. DFT calculations have also predicted that NHC-Ru-catalyzed olefin isomerization arising from substrate-induced decomposition of the second-generation Grubbs catalyst should be more facile than in the case of the first-generation catalyst; see: W. J. van Rensburg, P. J. Steyberg, W. H. Meyer, M. M. Kirk, G. S. Forman, *J. Am. Chem. Soc.* **2004**, *126*, 14332–14333.

[23] An interesting acceleration effect of phenol as an additive for olefin metathesis has been reported; see: G. S. Forman, A. E. McConnell, R. P. Tooze, W. J. van Rensburg, W. H. Meyer, M. M. Kirk, C. L. Dwyer, D. W. Serfontein, *Organometallics* **2005**, *24*, 4528–4542. In the present enyne metathesis, similar activation of the catalyst by an allylic hydroxy group might act in the same way as phenol.

[24] Details of the synthesis of enyne substrates are given in the Supporting Information.

[25] W. Herz, R.-R. Juo, *J. Org. Chem.* **1985**, *50*, 618–627.

[26] Detailed data of the kinetic studies are given in the Supporting Information.

Received: July 16, 2008
Published online: October 10, 2008

