

Acceleration effect of allylic hydroxy group on ring-closing enyne metathesis of terminal alkynes: scope and application to the synthesis of isofagomine

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Abstract

An interesting allylic substituent effect on ring-closing enyne metathesis has been found. An allylic hydroxy group on enyne substrates accelerates ring-closing enyne metathesis of terminal alkynes. The reaction proceeds smoothly without ethylene atmosphere and/or more reactive newer generation Ru-carbene catalysts, which are generally necessary to promote the reaction. This efficient reaction was applied to the synthesis of isofagomine.

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Enyne metathesis between an alkyne and an alkene is a powerful and highly atom-economical carbon–carbon bond forming reaction to generate 1,3-dienes,¹ which can be transformed into more complex organic molecules.² With the advent of Ru-alkylidene catalysts,³ applications of both intramolecular ring-closing and intermolecular cross enyne metathesis have rapidly expanded.⁴ Despite its usefulness, however, the development of enyne metathesis has lagged behind that of olefin metathesis,⁵ probably due to its capricious efficiency. The ring-closing enyne metathesis of terminal alkynes using Grubbs' 1st generation catalyst (Fig. 1, cycle A) is often slow, and the Ru-vinylcarbene intermediate (IM-2) is thought to prevent the catalytic cycle because of its stability.^{7,8} This drawback has been overcome by utilizing an ethylene atmosphere to regenerate reactive Ru-carbene species into a new catalytic cycle (Fig. 1, cycle B)^{7,9} and/or by developing new more reactive catalysts.¹⁰ In this Letter, we report an interesting substituent effect on ring-closing enyne metathesis, which

also can resolve the efficiency problem of enyne metathesis. Introduction of an allylic hydroxy group into a variety of enyne substrates smoothly promoted the enyne metathesis of terminal alkynes without ethylene atmosphere and/or more reactive newer generation catalysts. This efficient reaction was applied to the synthesis of isofagomine.

In conjunction with our continuous studies on aza-sugars,¹¹ we investigated enyne metathesis of N-containing enyne substrates (**1a–d**) to construct a 3-piperidine framework. The enyne substrates were treated with Grubbs' 1st generation catalyst (4 mol %) in CH₂Cl₂ at rt. The results

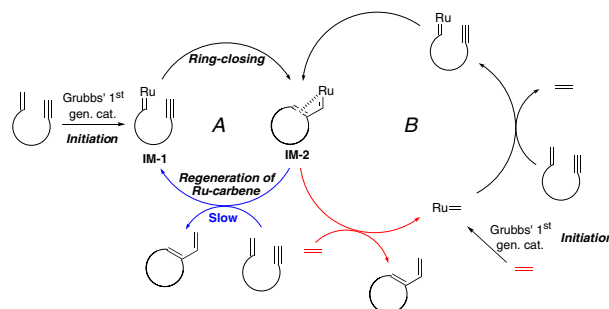
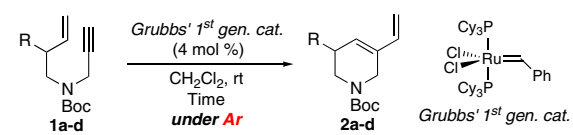


Fig. 1. Catalytic cycle of ring-closing enyne metathesis of terminal alkynes and the acceleration effect of ethylene.^{6,9}

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Table 1
Acceleration effect of allylic hydroxy group

				
Entry	R	Time (h)	Products	Yield ^{a,b} (%)
1	H (1a)	41	2a	32 (41)
2 ^c	H (1a)	1.5	2a	96
3	OH (1b)	1.5	2b	>99
4	OBn (1c)	41	2c	44 (32)
5	OTBDPS (1d)	41	2d	7 (73)

^a Isolated yield.

^b Figures in parentheses are recovery yields estimated from ¹H NMR spectrum of crude reaction mixture.

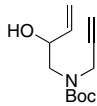
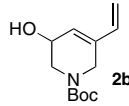
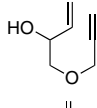
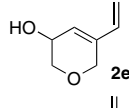
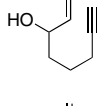
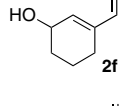
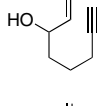
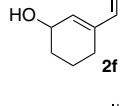
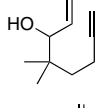
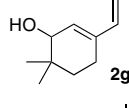
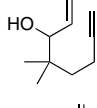
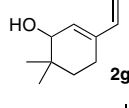
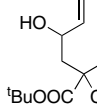
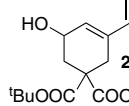
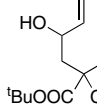
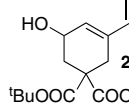
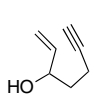
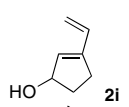
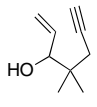
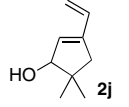
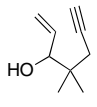
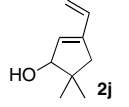
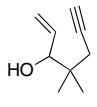
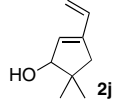
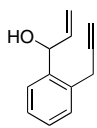
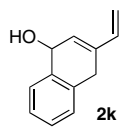
^c The reaction was performed under ethylene atmosphere.

are summarized in Table 1. An interesting effect of the allylic hydroxy group has been highlighted from them. Compared with the substrate *without* an allylic substituent (**1a**), enyne metathesis of the substrate *with* an allylic hydroxy group (**1b**) proceeded rapidly (Table 1, entries 1 and 3). This acceleration effect of an allylic hydroxy group is comparable to the effect of an ethylene atmosphere (Table 1, entry 2). Also, the acceleration is specific for an allylic hydroxy group. Protection of the allylic hydroxy group decreased the reaction rate and 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. Using 4 mol % of Grubbs' 1st generation catalyst, ring-closing metathesis of various N-, O-, C-tethered enynes containing an allylic hydroxy group was investigated in CH₂Cl₂ at rt (Table 2). The enyne metathesis of an O-tethered enyne that constructs a six-membered cyclic 1,3-diene proceeded with excellent yield (99%) in a short time (Table 2, entry 2). C-Tethered enynes with and without substituents on the tethered chain smoothly promoted ring-closing enyne metathesis to afford five- and six-membered cyclic products (Table 2, entries 3–12). Although some reactions took a long time and had low efficiency, with higher catalyst loading almost all of these reactions were completed in a short time and gave cyclic products in good yields. The reaction of a benzene ring-tethered enyne also proceeded smoothly to yield a bicyclic product (**2k**) in excellent yield (Table 2, entry 13). Unfortunately, seven-membered ring products were not obtained from corresponding N-, O-, C-tethered enynes (Table 2, entries 14–16). Although there are some limitations, the enyne metathesis of terminal alkynes with an allylic hydroxy group proceeds smoothly without ethylene atmosphere and/or more reactive newer generation catalysts. The acceleration effect is applicable to a wide range of substrates.

Utilizing this efficient reaction, the synthesis of isofagomine was demonstrated (Scheme 1). Isofagomine is a potent selective β-glucosidase inhibitor that has recently

Table 2
Scope of the acceleration effect of allylic group^a

Entry	Substrate	Time (h)	Products	Yield ^{b,c} (%)
1		1.5		>99
2		1.5		99
3		44.5		74 (17)
4 ^d		1		66
5		32		>99
6 ^d		5		66
7		48.5		76
8 ^d		3		77
9		4		79
10		44		15
11 ^d		16.5		45
12 ^e		1.5		61
13		1		>99 ^f
14	1l : X = NBoc, Y = CH ₂	48	2l	nd ^g
15	1m : X = CH ₂ , Y = O	30	2m	nd ^g
16	1n : X = CH ₂ , Y = C(COOEt) ₂	40	2n	nd ^g

^a The reactions were performed with 0.002 M of Grubbs' 1st generation catalyst.

^b Isolated yield.

^c Figures in parenthesis are recovery yields estimated from ¹H NMR spectrum of crude reaction mixture.

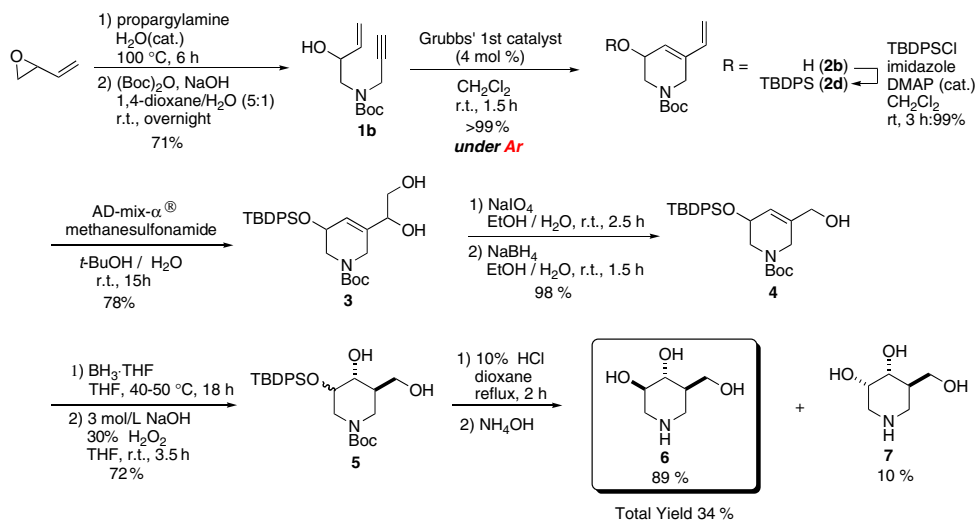
^d 8 mol % of the catalyst (0.002 M) was used.

^e 12 mol % of the catalyst (0.002 M) was used.

^g nd = not detected.

^f Since **2k** is easily transformed to 2-vinylnaphthalene, the yield was calculated from the sum of **2k** and 2-vinylnaphthalene (**2k**: 2-vinylnaphthalene = 74:26). After 14 h, **2k** was completely converted to 2-vinylnaphthalene.

received much attention in Gaucher's disease therapy.¹² The hydroxy group of dienol **2b** given by the ring-closing metathesis (>99%) was protected with a *tert*-butyldiphenylsilyl (TBDPS) group (99%). Then 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 with NaIO₄ followed by reduction with NaBH₄ gave allyl alcohol **4** (98% for two steps). Hydroboration of the internal olefin and the introduction of a hydroxy group provided



Scheme 1. Application to isofagomine synthesis.

diol **5** (72% for two steps). After deprotection of the TBDPS and the *tert*-butoxycarbonyl (Boc) group with 10 mol % HCl, isofagomine (**6**, 89%) and 3-epi-isofagomine (**7**, 10%) were obtained.¹³ Isofagomine (**6**) was synthesized in 34% total yield from commercially available 1,3-butadiene monoxide.^{14,15}

In summary, we have found an interesting acceleration effect of an allylic hydroxy group on ring-closing enyne metathesis.^{16–18} The ring-closing enyne metathesis of various terminal alkynes containing an allylic hydroxy group proceeded smoothly without ethylene atmosphere and/or more reactive newer generation Ru-carbene catalysts.¹⁹ We believe that enyne metathesis would be more helpful and would act as familiar tool in organic synthesis using this acceleration effect. Further investigations of the mechanism of the acceleration are currently under way.²⁰ Also, the application of this acceleration effect to other systems and the development of selective molecular transformations using this acceleration effect are proceeding in our laboratory.

Acknowledgments

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13. This anti-selectivity would be induced by steric repulsion of TBDPSO group in the hydroboration step.
14. The use of AD-mix- α [®] would induce slight kinetic resolution of **3** and $[\alpha]_{\text{D}}^{27} -1.8$ (*c* 1.43, CHCl₃) was indicated for the final product **6**. Compound **6**: $[\alpha]_{\text{D}}^{27} -1.8$ (*c* 1.43, CHCl₃); ¹H NMR (600 MHz, D₂O) δ (ppm): 1.61–1.68 (m, 1H), 2.33–2.38 (m, 2H), 3.05 (dd, *J* = 13.0, 3.5 Hz, 1H), 3.10 (dd, *J* = 12.1, 4.8 Hz, 1H), 3.27 (t, *J* = 9.9 Hz, 1H), 3.43–3.48 (m, 1H), 3.59 (dd, *J* = 11.4, 7.0 Hz, 1H), 3.78 (dd, *J* = 11.4, 3.3 Hz, 1H); ¹³C NMR (100 MHz, D₂O/CH₃CN) δ (ppm): 43.9, 45.7, 48.8, 59.8, 71.4, 73.1; EI-MS (*m/z*): 147 (*M*⁺); HRMS: calcd for C₆H₁₃NO₃: 147.0895, found: 147.0845.
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18. Effects of other substituents on the rate of Ru-carbene catalyzed enyne metathesis, see: (a) Galan, B. R.; Giessert, A. J.; Keister, J. B.; Diver, S. T. *J. Am. Chem. Soc.* **2005**, *127*, 5762–5763; (b) Kinoshita, T.; Sato, Y.; Mori, M. *Adv. Synth. Catal.* **2002**, *344*, 678–693.
19. An interesting acceleration effect of phenol as an additive for olefin metathesis has been reported. See: Forman, G. S.; McConnell, A. E.; Tooze, R. P.; Janse van Rensburg, W.; Meyer, W. H.; Kirk, M. M.; Dwyer, C. L.; Serfontein, D. W. *Organometallics* **2005**, *24*, 4528–4542. In the present enyne metathesis, the allylic hydroxy group might act in the same way as phenol.
20. *General procedure for allylic hydroxy group accelerated ring-closing enyne metathesis*: To a solution of an enyne substrate containing an allylic hydroxy group in CH₂Cl₂ was added 4, 8 or 12 mol % of Grubbs' 1st generation catalyst at rt under Ar atmosphere. The concentration of Grubbs' 1st generation catalyst was kept at 0.002 M. The mixture was stirred for the indicated reaction time. Then the reaction mixture was concentrated in vacuo and the residue was purified with silica gel column chromatography to obtain cyclic 1,3-dienes. Spectroscopic data for representative examples: Compound **2b**: ¹H NMR (600 MHz, CDCl₃/TMS) δ (ppm): 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 (dd, *J* = 17.6, 11.0 Hz, 1H); ¹³C NMR (67.5 MHz, C₆D₆, 60 °C) δ (ppm): 28.5, 43.0, 48.2, 64.2, 79.8, 113.1, 130.3, 135.7, 136.7, 155.1; IR (neat): 1683, 3406 cm⁻¹; EI-MS (*m/z*): 225 (*M*⁺); HRMS: calcd for C₁₂H₁₉NO₃: 225.1365, found: 225.1370. Compound **2f**: ¹H NMR (400 MHz, CDCl₃) δ (ppm): 1.56–1.64 (m, 2H), 1.71 (br s, 1H), 1.79–1.90 (m, 2H), 2.11–2.15 (m, 2H), 4.29 (br s, 1H), 5.04 (d, *J* = 10.7 Hz, 1H), 5.20 (d, *J* = 17.6 Hz, 1H), 5.75 (br s, 1H), 6.34 (dd, *J* = 17.6, 10.7 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ (ppm): 18.8, 23.7, 32.0, 66.2, 112.9, 130.8, 138.6, 139.2; IR (neat): 909, 991, 1049, 1607, 2863, 2935, 3308 cm⁻¹; EI-MS (*m/z*): 124 (*M*⁺); HRMS: calcd for C₈H₁₂O: 124.0888, found: 124.0889. Compound **2h**: ¹H NMR (400 MHz, CDCl₃) δ (ppm): 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 (br s, 1H), 5.10 (d, *J* = 10.6, 1 H), 5.30 (d, *J* = 17.9 Hz, 1H), 5.76 (br s, 1H), 6.53 (dd, *J* = 17.4, 11.1 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ (ppm): 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; IR (neat): 1147, 1257, 1369, 1608, 1716, 1729, 2934, 2978, 3522 cm⁻¹; EI-MS (*m/z*): 324 (*M*⁺); HRMS: calcd for C₁₈H₂₈O₅: 324.1937, found: 324.1947.