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Highly regioselective synthesis of cyclic enol silyl ethers using ring-closing metathesis

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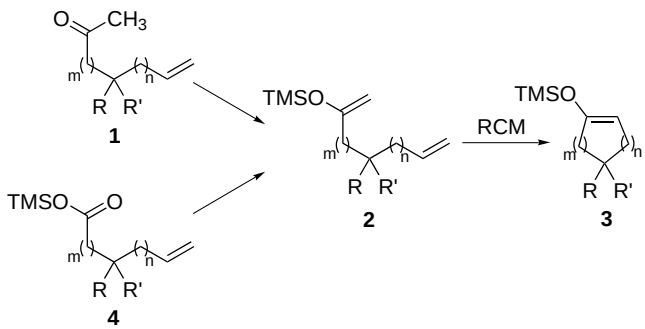
Abstract—We developed the first highly regioselective synthesis of cyclic enol ethers from readily accessible acyclic alkenyl ketones or acyclic alkenyl silyl esters using ring-closing metathesis (RCM). The RCM of acyclic enol silyl ethers was examined using Tebbe reagent **5** or Grubbs catalyst **6** or **7** and successfully proceeded using the second generation Grubbs catalyst **7** to afford the corresponding cyclic enol ethers in high yield (up to 99%, two steps from alkenyl kenone). This process can be applied to syntheses of a variety of cyclic enol ethers in a highly regioselective manner.

Despite their utility and versatility in organic synthesis,[1] the regioselective synthesis of cyclic enol silyl ethers is still a challenging transformation. For example, the enolate formation of cyclic ketone with strong base followed by trapping with silyl chloride, which is one of the simplest and most conventional methods, often produces a mixture of regioisomers.[2] Poor regioselectivity is a common problem encountered in the course of synthetic studies of bioactive natural and unnatural compounds. Therefore, the development of efficient methods to synthesize enol silyl ether in a highly regioselective manner from a readily accessible starting material is very desirable. We hypothesized that ring-closing metathesis (RCM) between an acyclic enol silyl ether and the internal terminal olefin might be exploited in a novel way to regioselectively produce the desired cyclic enol silyl ether under mild conditions. RCM is a powerful strategy for organic synthesis.[3] Despite the successes of this general approach to ring construction, there are few reports of the RCM of enol ethers. In 1996, Nicolaou et al. achieved direct conversion of alkenyl esters to cyclic enol ethers with Tebbe reagent **5**.[4,5] However, no RCM of enol silyl ethers to cyclic enol silyl ethers has been reported, probably due to the instability of enol silyl ethers. Herein we present a new strategy for the synthesis of a variety of cyclic enol silyl ethers **3** by intramolecular RCM between the double bond of the enol silyl ether moiety and the internal terminal olefin (Scheme 1). Using this strategy, many types of cyclic enol silyl ethers **3** can be synthesized in a highly regioselective manner from readily accessible acyclic alkenyl ketones **1** or acyclic alkenyl silyl esters **4** under mild conditions.

To explore the possibilities of this strategy, we first examined RCM of enol silyl ether **10**, which was prepared in situ from the corresponding silyl ester **8**.[6] According to Nicolaou's procedure, **8** was treated with excess Tebbe reagent **5** (Fig. 1). Initially, acyclic enol silyl ether **10** was formed at lower temperatures (−78°C



Scheme 1.

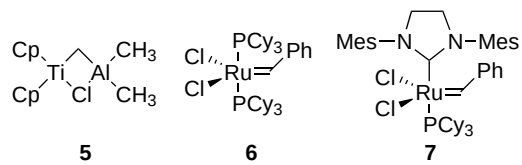


Figure 1. Structures of Tebbe reagent **5**, Grubbs catalyst **6**, and the second generation Grubbs catalyst **7**.

Keywords: ring-closing metathesis; enol silyl ether; Grubbs catalyst.

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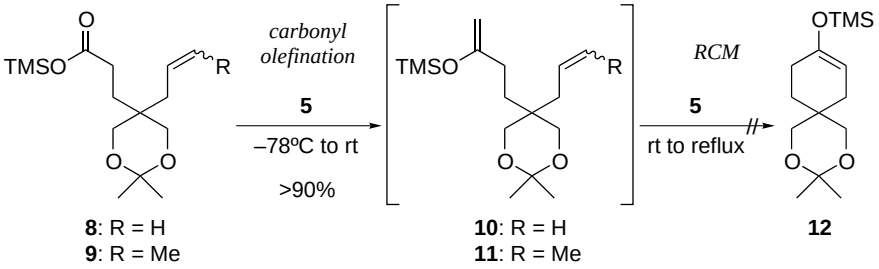
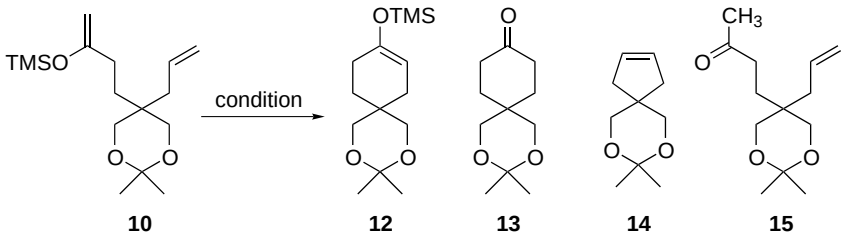


Scheme 2. Carbonyl olefination/RCM cascade reaction using Tebbe reagent **5**.

Table 1. RCM of acyclic enol ether **10** using Grubbs catalyst **6** or **7**



Entry	Catalyst (mol%)	Solvent (conc.)	Temp.	Time (h)	Yield (%)			
					12[a]	**13**[a]	**14**[b]	**15**[b]
1[c]	**6** (40)	CH_2Cl_2 (0.01 M)	rt	72	0		23	68
2[c]	**6** (37)	Benzene (0.01 M)	rt	120	Trace		10	65
3[d]	**6** (10)	Benzene (0.01 M)	Reflux	48	0		17	
4[d]	**6** (80)	Benzene (0.01 M)	rt	120	10	4	3	
5[d]	**7** (38)	CH_2Cl_2 (0.02 M)	Reflux	1	73			
6[c]	**7** (38)	CH_2Cl_2 (0.02 M)	Reflux	1	>99			
7[c]	**7** (50)	Benzene (0.02 M)	45°C	1	>99			

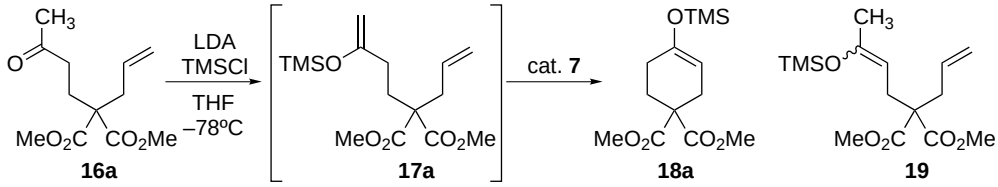
[a] Yield was determined by 500 MHz ^{1}H NMR (two steps from **8** or **15**).
[b] Isolated yield (two steps from **8** or **15**).
[c] **10** was prepared from **15** (LDA, TMSCl, THF, –78°C).
[d] **10** was prepared from **8** (Tebbe reagent, THF, –78°C).

to rt) in high yield.[7] At higher temperatures (rt to reflux in THF), however, only decomposition of **10** occurred instead of RCM (Scheme 2). Even using silyl ester **9** corresponding to Nicolaou's substrates, no desired product **12** was obtained. Probably the Tebbe reagent itself or a decomposed species promoted decomposition of the enol silyl ethers at the high temperature. Thus, we examined the use of Grubbs catalyst **6**[8] and the second generation Grubbs catalyst **7**[9] (Fig. 1) because of their high ability to promote the metathesis reaction. The results are summarized in Table 1. Surprisingly, in CH_2Cl_2 solution catalyst **6** promoted the migration of the double bond of the enol silyl ether moiety from *exo* to *endo* in preference to RCM to afford the undesired cyclic alkene **14** as a major byproduct with desilylated acyclic ketone **15** (entry 1). By changing the solvent from CH_2Cl_2 to benzene, this undesirable tendency was improved slightly and RCM proceeded to afford cyclic compounds **12** (10%) and **13** (4%), although 80 mol% of **6** was required (entry 4). In contrast, catalyst **7** successfully promoted RCM in both solvents to afford the corresponding cyclic enol silyl ether **12** in high yield (entries 5–7).

Further optimization of the reaction conditions was performed using enol silyl ether **17a**, which was readily prepared from the corresponding ketone **16a** (Table 2). In this case, the choice of solvent was critical. In CH_2Cl_2 solution even catalyst **7** promoted migration of the double bond of the enol silyl ether moiety in high preference to RCM to afford **19** (entries 1–3). Finally, the use of benzene as a solvent under dilute condition (0.005 M) afforded the desired cyclic enol ether **18a** in almost quantitative yield (entry 7).[10]

Having succeeded in developing an efficient synthesis of cyclic enol silyl ether **18a** from acyclic alkenyl ketone **16a**, we examined the scope and limitation of different substrates. As shown in Table 3, catalyst **7** promoted RCM of a variety of acyclic enol silyl ethers **17a–e** to afford five- to seven-membered ring cyclic enol silyl ethers **18a–e** in good to excellent yield. In these cases, no migration of the double bond of the resulting cyclic enol silyl ethers **18** was observed, making this process a novel alternative method for the synthesis of cyclic enol silyl ethers in a highly regioselective manner. In addition, other types of substrates such as **19** and **22** were also converted to the desired cyclic enol ether **21** (90%,

Table 2. RCM of acyclic enol ether **17a** using Grubbs catalyst **7**



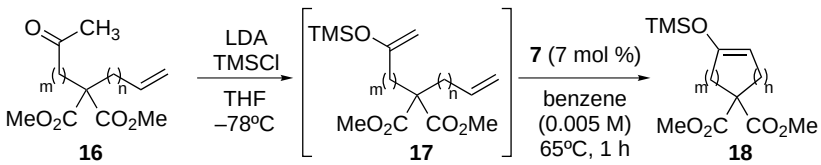
Entry	Catalyst (mol%)	Solvent (conc.)	Temp. (°C)	Time (h)	Yield (%)	
					18a[a]	**19**[a]
1	5	CH_2Cl_2 (0.1 M)	45	1.0	0	82
2	10	CH_2Cl_2 (0.01 M)	45	2.5	0	78
3	7	CH_2Cl_2 (0.001 M)	45	3.0	3	70
4	5	Benzene (0.05 M)	50	0.5	70	
5	7	Benzene (0.01 M)	50	1.0	92	
6	7	Benzene (0.005 M)	50	1.0	97	
7	7	Benzene (0.005 M)	65	1.0	99	
8	7	Toluene (0.01 M)	50	1.0	95	

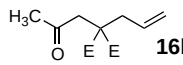
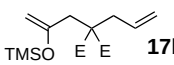
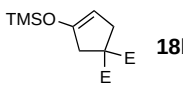
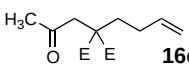
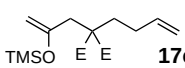
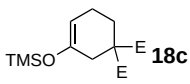
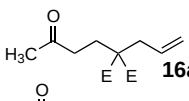
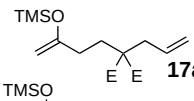
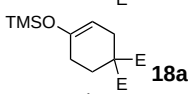
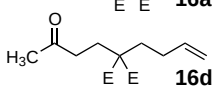
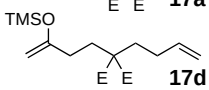
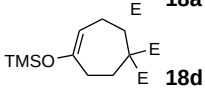
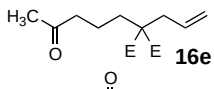
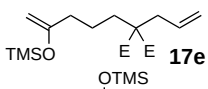
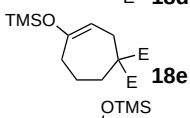
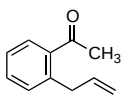
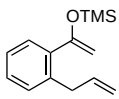
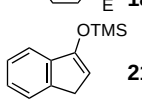
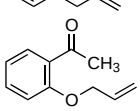
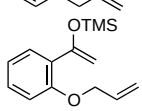
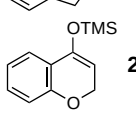
[a] Yield was determined by 500 MHz ^{1}H NMR (two steps from **16a**).

two steps) and **24** (92%, two steps), respectively. To the best of our knowledge, this is the first example of a synthesis of cyclic enol ethers from acyclic enol silyl ethers by using RCM.[11]

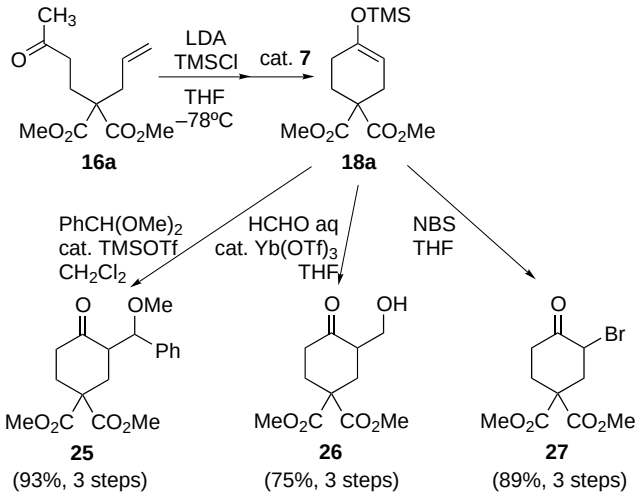
Finally, further transformation of cyclic enol silyl ether **18a** was demonstrated to confirm the yield and the regioselectivity (Scheme 3). Crude **18a**, which was almost pure after removal of the solvent under reduced pressure, was treated with benzaldehyde dimethyl acetal and a catalytic amount of trimethylsilyl triflate in CH_2Cl_2 to afford the coupling product **25** in 93% yield (three steps from **16a**).[12] In addition, an aldol reaction with aqueous formaldehyde solution[13] and bromination

Table 3. RCM of a variety of acyclic enol ethers using Grubbs catalyst **7**



Entry	Substrate (E = CO_2Me)	Intermediate	Product	Yield (%)[a]
1	 **16b**	 **17b**	 **18b**	94
2	 **16c**	 **17c**	 **18c**	92
3	 **16a**	 **17a**	 **18a**	99
4[b]	 **16d**	 **17d**	 **18d**	88
5[b]	 **16e**	 **17e**	 **18e**	93
6	 **19**	 **20**	 **21**	90
7	 **22**	 **23**	 **24**	92

[a] Yield was determined by 500 MHz ^{1}H NMR (2 steps from the corresponding acyclic ketone).
[b] The reaction was carried out in benzene (0.001 M) reflux condition.



Scheme 3. Transformation of cyclic enol ether **18a**.

proceeded to afford the corresponding desired products **26** (75%, three steps) and **27** (89%, three steps), respectively. Although overall yield of the transformation of **16a** to **26** was moderate, the RCM process under mild conditions appears to be a suitable candidate to synthesize β-hydroxy ketone instead of intramolecular nitrile oxide cyclo addition followed by treatment with Raney Ni.

In conclusion, we developed the first highly regioselective synthesis of cyclic enol silyl ethers from readily accessible acyclic alkenyl ketones or acyclic alkenyl silyl esters using RCM. By changing the catalyst from Grubbs catalyst **6** to the second generation Grubbs catalyst **7** and the solvent from CH_2Cl_2 to benzene, RCM of a variety of acyclic enol silyl ethers proceeds smoothly to afford the corresponding cyclic enol ethers in a highly regioselective manner. The described method renders many types of functionalized cyclic enol ethers readily available as a pure form in terms of regiochemistry. Further investigation concerning applications of this strategy to other kinds of metathesis and syntheses of complex bioactive compounds are currently ongoing.

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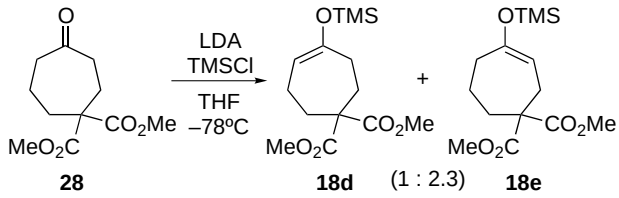
References

1. For recent reviews, see: (a) Fleming, I.; Barbero, A.; Walter, D. *Chem. Rev.* **1997**, *97*, 2063; (b) Carreira, E. M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. 3, pp. 998–1065.
2. For example, the enolate formation of cyclic ketone **28** with LDA followed by trapping with TMSCl gave a mixture of **18d** and **18e** (1:2.3).



3. For representative reviews on RCM, see: (a) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012; (b) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413; (c) Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995**, *28*, 446; (d) Schmalz, H.-G. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1833.
4. Nicolaou, K. C.; Postema, M. H. D.; Claiborne, C. F. *J. Am. Chem. Soc.* **1996**, *118*, 1565.
5. RCM reactions of enol ethers using Ru and Mo catalysts were also reported. For a representative example, see: Rainier, J. D.; Cox, J. M.; Allwein, S. P. *Tetrahedron Lett.* **2001**, *42*, 179 and references cited therein.
6. The alkenyl silyl esters **8** and **9** were prepared from the corresponding alkenyl carboxylic acids in high yield (>95%) according to the reported methods. See: Kita, Y.; Haruta, J.; Segawa, J.; Tamura, J. *Tetrahedron Lett.* **1979**, *20*, 4311.
7. The acyclic enol silyl ether **10** can be purified by quick silica gel column chromatography (92% isolated yield).
8. (a) Pchwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2039; (b) Pchwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100.
9. Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953. Second generation Grubbs catalyst **7** was prepared from Grubbs catalyst **6** according to the reference. We also used commercially available catalyst **7** (STREM Chemicals, Inc.), which had the same activity.
10. General procedure: To a solution of *i*-Pr_2NH (0.14 mL, 1.0 mmol) in THF (10 mL) was added 1.54 M hexane solution of *n*-BuLi (0.65 mL, 1.0 mmol) at 0°C. After 30 min, the reaction mixture was cooled to −78°C, to which TMSCl (0.32 mL, 2.46 mmol) and a solution of **16a** (198.7 mg, 0.82 mmol) in THF (5 mL) were added in order. After stirring at the same temperature for 2 h, the reaction was quenched by addition of saturated $NaHCO_3$ aqueous solution, allowed to warm to room temperature (rt), and concentrated in vacuo. The residue was treated with Et_2O and water, extracted with Et_2O twice. The combined organic layers were washed with water and brine, dried over Na_2SO_4 to afford the crude acyclic enol silyl ether **17a** (255 mg) (>99% yield determined by ^1H NMR): ^1H NMR (500 MHz) (benzene-d_6) δ 0.15 (s, 9 H), 2.19 (m, 2 H), 2.43 (m, 2 H), 2.83 (d, $J=7.3$ Hz, 2 H), 3.29 (s, 6 H), 4.13 (s, 1 H), 4.16 (s, 1 H), 4.97 (d, $J=10.7$ Hz, 1 H), 5.01 (d, $J=17.4$ Hz, 1 H), 5.74 (m, 1 H); ^{13}C NMR (125 MHz) (benzene-d_6) δ 0.0, 30.6, 31.9, 37.7, 51.9, 57.6, 90.2, 118.9, 132.9, 158.9, 171.3. To a solution of the crude **17a** (20.3 mg, 64.6 μmol) in benzene (13 mL, 0.005 M) was added catalyst **7** (3.8 mg, 4.5 μmol) under argon. The reaction mixture was stirred at 65°C for 1 h, then cooled to rt, and concentrated in vacuo to afford the

crude cyclic enol ether **18a** (22.2 mg) (99% yield determined by ^{1}H NMR): ^{1}H NMR (500 MHz) (benzene-d_6) δ 0.14 (s, 9 H), 2.19 (m, 2 H), 2.27 (t, $J=6.7$ Hz, 2 H), 2.78 (m, 2 H), 3.31 (s, 6 H), 4.88 (m, 1 H); ^{13}C NMR (125 MHz) (benzene-d_6) δ 0.2, 27.5, 28.6, 30.0, 52.1, 53.3, 101.2, 150.0, 171.6.

11. Recently, RCM of an acyclic enol silyl ether was achieved by: Arisawa, M.; Theeraladanon, C.; Nishida, A.; Nakagawa, M., independently. See: *18th International Congress of Heterocyclic Chemistry (Yokohama, Japan) Abstracts* **2001**, 130.
12. (a) Murata, S.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 2527; (b) Murata, S.; Suzuki, M.; Noyori, R. *J. Am. Chem. Soc.* **1980**, *102*, 3248.
13. (a) Kobayashi, S. *Chem. Lett.* **1991**, 2087; (b) Kobayashi, S.; Hachiya, I. *J. Org. Chem.* **1994**, *59*, 3590.