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Olefinic-ester cyclizations using Takai–Utimoto reduced titanium alkylidenes

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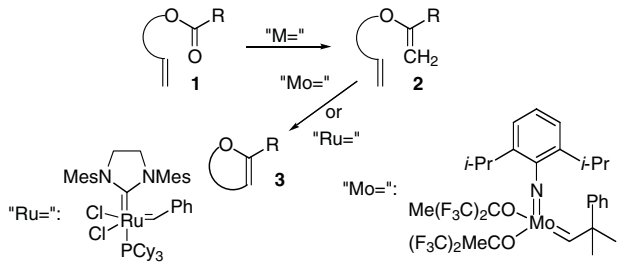
Abstract—The scope and limitations of the Takai–Utimoto reagent to induce the cyclization of olefinic-esters is described. Critical is the steric environment about both the ester and the olefin. Mechanistically, these results support the hypothesis that cyclized product comes from an olefin metathesis, carbonyl-olefination sequence.

Because they serve as precursors to a number of interesting heterocyclic compounds, cyclic enol ethers have garnered the attention of the chemical synthesis community. Among the various routes to their synthesis, there has been considerable interest in the conversion of olefinic-esters into cyclic enol ethers via the two-step metathesis sequence outlined in Scheme 1.[1,2]

Clearly, a more efficient method of transforming **1** into **3** would bypass acyclic enol ether intermediates (e.g., **2**). Along these lines, successes have been reported. In the mid-1980s Grubbs and co-workers successfully synthesized capnellene by utilizing norbornenes in a ring-opening metathesis, carbonyl-olefination sequence.[3] Subsequently, Fu and Grubbs reported the use of a tungsten alkylidene to generate cyclic enol ethers directly from an olefinic-ester.[4] Finally, Nicolaou and co-workers reported olefinic-ester cyclization reactions using the Tebbe and Petasis reagents to generate fused ether compounds.[5]



Scheme 1.

Our interest in cyclic enol ethers directed our attention to the generation of acyclic enol ethers from the corresponding olefinic-esters using the Takai–Utimoto titanium alkylidene.[6] We were attracted to this reagent primarily because of its in situ preparation and its diminished Lewis acidity relative to the more commonly employed Tebbe reagent. Important to the generation of highly substituted targets, substrates having functionality sensitive to the Tebbe reagent often stand up to the Takai–Utimoto reagent. For example, in our hands we were unable to isolate either acyclic or cyclic enol ethers from the reaction of **4** with the Tebbe reagent but were with the Takai–Utimoto reagent (Table 1).[7]

In addition to demonstrating the mild nature of the Takai–Utimoto protocol, the example in Table 1 illustrates that this reagent can affect the cyclization of olefinic-esters.[8] However, Scheme 2 also points to a significant problem; to the best of our knowledge, the exclusive formation of cyclic enol ethers from olefinic-esters using this reagent has not been reported. A better understanding of the ability of the Takai–Utimoto reagent to convert olefinic-esters into cyclic enol ethers would be significant; the results of our initial attempts to attain this goal are described here.

In their work, Nicolaou and co-workers found that cyclic enol ethers resulted from acyclic enol ether intermediates

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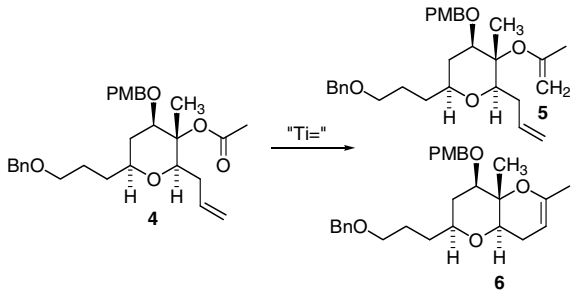
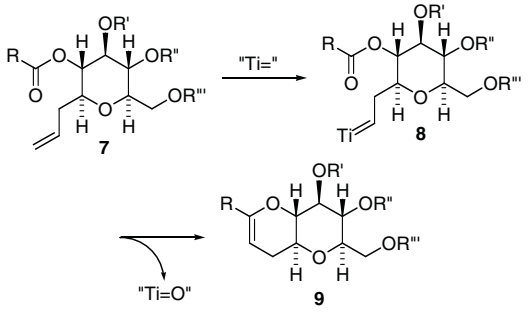
Table 1.



'Ti ='	Yield (%)	5:6
Tebbe	—[a]	—
Takai	77[b]	1:1

[a] Products included hydrolyzed ester.
[b] Yield after a subsequent RCM reaction using the 2nd generation Grubb's catalyst.

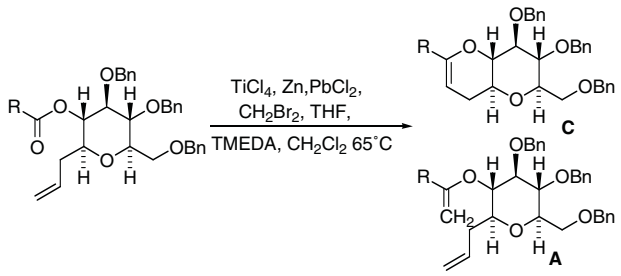


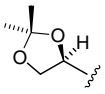
Scheme 2.

and a subsequent enol ether-olefin RCM sequence.[5] In contrast, we found that acyclic enol ethers are not precursors to cyclic enol ethers when the Takai–Utimoto reagent is used.[9] Based upon this, we proposed that cyclic material from the Takai–Utimoto reagent was the result of an olefin metathesis, carbonyl-olefination sequence (Scheme 2). Mechanistically, this proposal is similar to the initial Grubbs hypothesis;[3] the difference being that Grubbs had only reported the use of strained olefins.

If our hypothesis were accurate, one would predict that the relative steric environment about the ester would influence the amount of cyclic material produced. To test this, we turned to β-*C*-glycosides derived from tris-benzylidene-D-glucal.[10] Surprisingly, with acetate (R = CH_3), isobutyrate (R = *i*-Pr), and TBDPS protected glycolate (R = CH_2OTBDPS) esters **10**–**12**, substitution had no effect on the relative amount of cyclic and acyclic products **14**–**16** (entries 1–3). In contrast, when dimethyldioxolane ester **13** was exposed to the Takai–Utimoto reagent, cyclic enol ether **17** was formed exclusively (entry 4). To the best of our knowledge, the cyclization of **13** represents the first highly selective olefinic-ester cyclization reaction utilizing the Takai–Utimoto reagent. As the dimethyldioxolane ester is larger than the other esters, we believe that this result is consistent with our mechanistic hypothesis (Table 2).[11]

Table 2.



Entry	Ester	R	Enol ether(s)	Yield (%)[a]	C:A[b]
1	**10**	CH_3	**14**	80	5:3
2	**11**	*i*-Pr	**15**	88	2.4:1
3	**12**	CH_2OTBDPS	**16**	86	2.1:1
4	**13**		**17**	71	>95:5

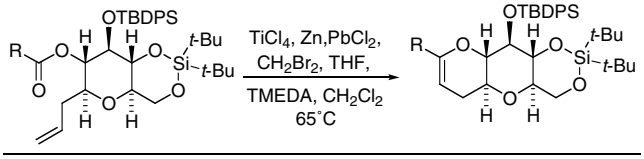
[a] Isolated yields after chromatography.
[b] From the crude ^{1}H NMR of the reaction mixture.

Interestingly, the steric environment on the pyranyl side of the ester played an even larger role in the generation of cyclic enol ether (Table 3). Substrates having C(3) TBDPS ethers gave exclusively cyclic products even when relatively unhindered esters were employed.

Cyclizations of α-allyl *C*-glycosidic esters are also sensitive to the steric environment about the ester (Table 4).[12] That is, **23** gave exclusively *cis*-fused bicyclic enol ether **25** while **22** (R = CH_3) gave a mixture of cyclic and acyclic enol ethers.

To determine the extent to which a TBDPS ether at C(3) was capable of influencing the cyclization, we examined glycosides having dialkyl substitution at the anomeric position (*C*-ketosides, Table 5). Based upon our mechanistic hypothesis, it was not surprising that *C*-ketosides gave relatively lower yields of cyclic products. However, as was observed previously, the dimethyldioxolane-substituted ester **27** gave cyclic enol ether **29** as the only observed enol ether product (entry 2). Because both the olefin and ester are hindered in **27**, it is not surprising that the reaction was sluggish; the remainder of the isolable material (26%) consisted of the recovered starting material.

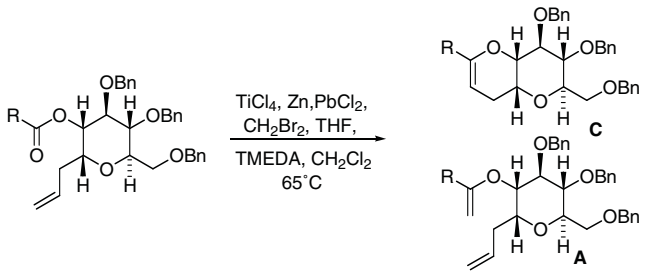
Table 3.



Entry	Ester	R	Enol ether	Yield (%)[a]	C:A[b]
1	**18**	CH_3	**20**	84	>95:5
2	**19**	*i*-Pr	**21**	89	>95:5

[a] Isolated yields after chromatography.
[b] From the crude ^{1}H NMR of the reaction mixture.

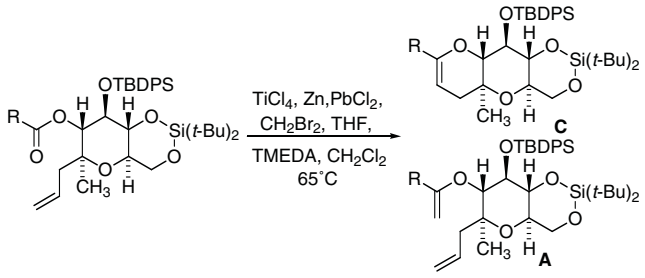
Table 4.

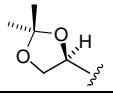


Entry	Ester	R	Enol ether(s)	Yield (%)[a]	**C**:**A**[b]
1	**22**	CH_3	**24**	84	1:2.8
2	**23**	*t*-Bu	**25**	70	>95:5

[a] Isolated yields after chromatography.
[b] From the crude ^{1}H NMR of the reaction mixture.

Table 5.



Entry	Ester	R	Enol ether(s)	Yield (%)[a]	**C**:**A**[b]
1	**26**	$CH_2OTBDMS$	**28**	77	1.3:1
2	**27**		**29**	66[c]	>95:5

[a] Isolated yields after chromatography.
[b] From the crude ^{1}H NMR of the reaction mixture.
[c] 26% recovered **27**.

In summary, we have shown that olefinic-ester cyclization reactions using the Takai–Utimoto reagent protocol are dependent upon the steric environment about both the ester and olefin. These observations are consistent with the olefin metathesis, carbonyl-olefination reaction mechanism that was proposed previously. We are continuing to explore these reactions including their use in total synthesis problems.

Acknowledgments

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Supplementary data

Experimental procedures and spectroscopic data for all new compounds. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.08.071.

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