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Olefinic Ester and Diene Ring-Closing Metathesis Using a Reduced Titanium Alkylidene

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Because of their inherent reactivity, cyclic enol ethers serve as precursors to a number of interesting heterocyclic compounds and have garnered the attention of the chemical synthesis community. Among the variety of methods that have been reported for their synthesis, there has been considerable interest in the cyclization chemistry of olefinic esters 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, Stille, and Santarsiero successfully synthesized capnellene by utilizing strained olefinic esters (norbornenes) in ring-opening metathesis, carbonyl olefination reactions.³ Subsequently, Grubbs and Fu reported the use of a tungsten alkylidene to generate a cyclic enol ether directly from an acyclic olefinic ester.⁴ In 1996, Nicolaou and co-workers reported olefinic ester cyclization reactions using the Tebbe and Petasis reagents to generate fused ether compounds.⁵ While Nicolaou's results were certainly impressive, the applicability of these reagents in olefinic ester cyclizations appears to be limited. A number of groups including ours have reported the reactions to be capricious and to lead, with some substrates, to a multitude of undesired side products.⁶

As a means of generating polycyclic ether natural products, we have also been interested in olefinic ester cyclizations and have employed the Takai–Utimoto reduced titanium reagent largely because of its in situ preparation, its increased reactivity relative to the Petasis reagent, and its diminished Lewis acidity relative to the Tebbe reagent.^{7,8} Although we previously described the use of this reagent to affect olefinic ester cyclizations, the reactions were limited to sterically hindered esters and relatively unhindered olefins.^{9,10} In contrast to these results, during our recent work targeting the generation of the B ring of gambieric acid A, we were surprised to find that the product distribution (acyclic vs cyclic enol ether) from the reaction of the reduced titanium alkylidene reagent was dependent upon the alkylidene reagent used (Scheme 2).¹¹ That is, the titanium methylidene reagent that comes from the use of dibromomethane as the alkylidene source gave only acyclic enol ether while the corresponding ethylidene reagent from dibromoethane gave only cyclic enol ether. That substitution on the titanium alkylidene reagent could be used to direct reactivity was, to the

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Supporting Information Available: General experimental procedure for the cyclization reaction and spectroscopic data for all new cyclic compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

best of our knowledge, unprecedented and in our opinion deserving of further study. Outlined here are our preliminary experiments aimed at uncovering the scope of this result.

We initially chose to examine whether the reduced titanium ethylidene reagent could affect the cyclization of olefinic ester **10**. We had previously examined the reaction of **10** with the corresponding titanium methylidene reagent and had found it to give a mixture of products (Table 1, entry 1).⁸ In a similar fashion to the results with **8**, when we subjected **10** to the titanium ethylidene reagent, we isolated cyclic enol ether **12** as the only identifiable product in 75% yield (entry 2). We next explored the reaction on a more challenging substrate, olefinic ester **13**, lacking a preformed cyclic template. When **13** was subjected to the titanium ethylidene reaction conditions, we isolated cyclic enol ether **15** as the only product in 70% yield (Table 1, entry 4). In contrast to this result, the corresponding methylidene reagent gave a 1:1 mixture of cyclic and acyclic enol ethers in 70% yield (entry 3). To get a better sense of the reaction scope, we also examined acyclic templates **16** and **18**.^{2c} Both substrates underwent successful cyclization to give dihydropyran **17** and oxepene **19**, respectively (Table 1, entries 5 and 6).

Assuming titanium alkylidenes to be involved in the olefinic ester chemistry outlined above, we became intrigued by the possibility that the titanium reagent might also induce diene ring-closing metathesis (RCM) cyclizations. With the exception of Nicolaou's enol ether-olefin RCM chemistry,⁵ to the best of our knowledge, there are no reports of unstrained dienes undergoing RCM reactions using titanium alkylidenes.¹² In light of this, we were pleasantly surprised to isolate spirocyclic allyl ether **21**¹³ in quantitative yield when diene **20** was subjected to the titanium ethylidene reagent (Table 2, entry 1). Impressively, this transformation even proceeded at room temperature. We were also pleased to be able to generate dihydropyran **23**,¹⁴ oxepene **25**,¹⁵ and oxocene **27**¹⁶ from the reactions of the titanium ethylidene reagent with the acyclic allyl ethers **22**, **24**, and **26**, respectively (Table 2, entries 2–4).

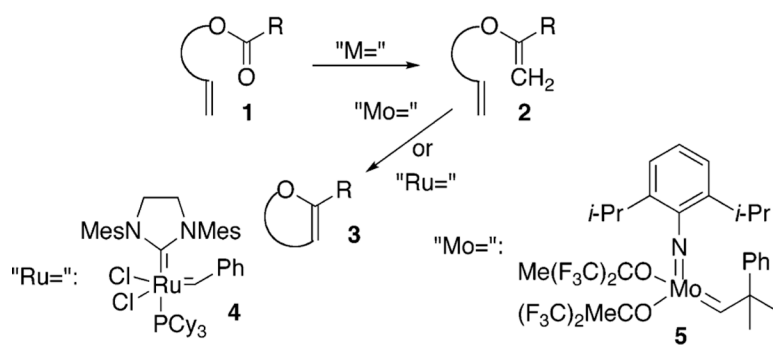
In summary, this communication has described the unique and unprecedented reactivity of an in-situ-generated reduced titanium ethylidene reagent. Although optimization of both olefinic ester and diene RCM cyclization reactions is clearly required, for example, we have not explored the effect of stoichiometry or additives nor have we focused on the scale-up of the reaction (the largest scale carried out thus far in our hands has been 0.5 g), we believe that these studies represent a significant breakthrough. The reduced titanium reagent described here is relatively inexpensive, it is generated in situ, and it is tolerant of a wide variety of functionality.^{1c} We intend to continue to study the scope of its reactivity.

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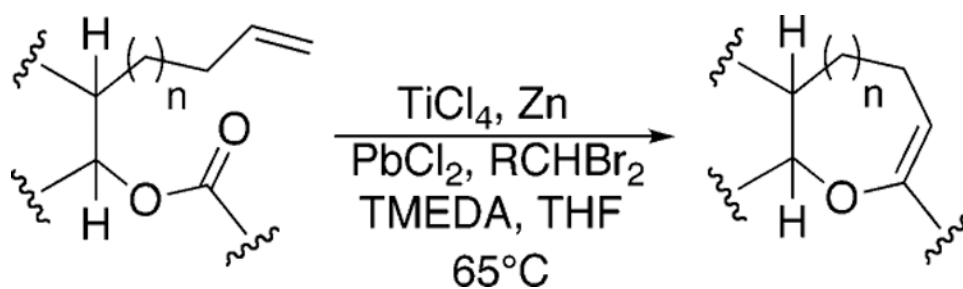
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Scheme 1.

Table 1.

Olefinic Ester Cyclizations

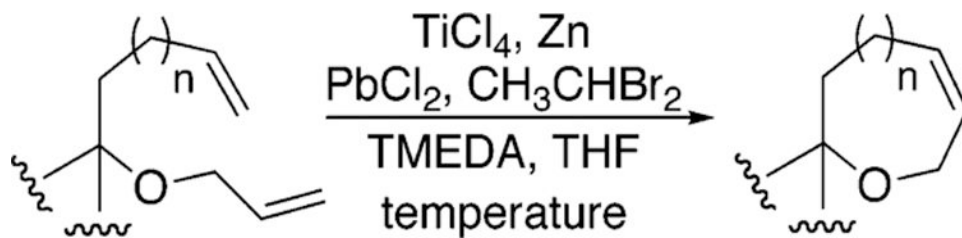


entry	starting material/acyclic enol ether	RCHBr ₂	cyclic enol ether	yield (cyclic:acyclic)
1	<p>10: X = O 11: X = CH₂</p>	CH ₂ Br ₂	<p>12</p>	80% (5:3)
2	10	CH ₃ CHBr ₂	12	75% (>95:5)
3 ^a	<p>13: X = O 14: X = CH₂</p>	CH ₂ Br ₂	<p>15</p>	70% (1:1)
4	13	CH ₃ CHBr ₂	15	70% (>95:5)
5	<p>16</p>	CH ₃ CHBr ₂	<p>17</p>	78% (>95:5)
6	<p>18</p>	CH ₃ CHBr ₂	<p>19</p>	82% (>95:5)

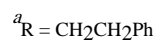
^aR = CH₂CH₂CH₂CH(OMe)₂, R' = CH₂CH₂CH₂OTBDPS

Table 2.

Reduced Titanium-Mediated Diene RCM



entry	starting material ^a	temp	product ^a	yield
1	 20	65 °C or rt	 21	100%
2	 22	rt	 23	81%
3	 24	65 °C	 25	72%
4	 26	65 °C	 27	60%



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