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New Tandem Catalysis: Preparation of Cyclic Enol Ethers through a Ruthenium-Catalyzed Ring-Closing Metathesis−Olefin Isomerization Sequence

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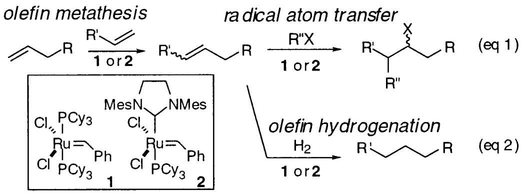
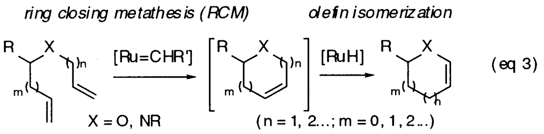
Reactions run in tandem can generate desired targets efficiently in a single reaction vessel without the need to purify at each step.[1] A particularly attractive tandem process occurs when two or more sequential reactions are mediated by the same catalytic precursor. The ability of Grubbs' ruthenium alkylidenes (**1** and **2**) to function as procatalysts for olefin metatheses,[2] atom-transfer reactions (eq 1), and olefin hydrogenations (eq 2) has led to several examples where combinations of these transformations provide efficient new entries into useful products.[3]



During studies on new olefin metatheses, we noted that olefin isomerizations interfere occasionally with the metathesis process. This observation has been reported by others and has been exploited recently in a deprotection of allyl ethers and amines.[4] Unfortunately, the ruthenium species derived from the Grubbs' catalyst responsible for this activity is unclear. While commercially available, unpurified ruthenium alkylidenes can effect the isomerization reaction, purified alkylidenes possess only the metathesis activity.[5]

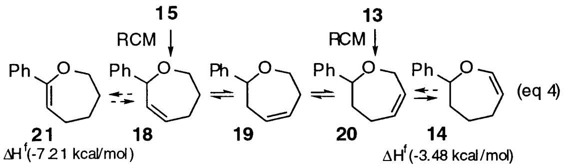
To address the unpredictable and sporadic nature of the transformation, we sought to determine modifications to the ruthenium complex that facilitate the olefin isomerization relative to other processes. Moreover, identifying conditions that isomerize olefins selectively offers the opportunity to execute sequentially an olefin metathesis and an olefin isomerization in one reaction vessel with the addition of only one metal precursor. *Toward this objective, we report herein a new tandem process that generates cyclic enol ethers through a ruthenium alkylidene-catalyzed ring-closing metathesis (RCM) of acyclic dienes followed by a ruthenium hydride-catalyzed olefin isomerization of the resulting RCM products (eq 3).*



Cyclic enol ethers play a vital role in the synthesis of bioactive compounds such as glycals,[6] polyether antibiotics and natural products,[7] and nucleoside antibiotics.[8] A number of groups have exploited RCM as a methodology to synthesize such ethers. Direct access into enol ethers had been limited initially to Mo[9] or Ti reagents.[10] Traditionally, vinyl ethers have been poor substrates in Ru-catalyzed olefin metatheses; however, in recent years several groups have developed successful RCM approaches toward cyclic enol ethers.[11,12] In this communication we describe a tandem protocol; a RCM−olefin isomerization that affords cyclic enol ethers *directly* from easily prepared dienes.[13]

Identifying reaction conditions that convert reliably the metathesis-active ruthenium alkylidene into an isomerization catalyst was the first step in developing the tandem process. Solvents, including benzene and methylene chloride, with a series of additives, such as HCO_2H, $NaBH_3CN$, NaOMe/MeOH, and H_2 were screened for their ability to enhance the olefin isomerization activity of complexes **1** and **2**. This study revealed that the treatment of ruthenium alkylidene **2** in CH_2Cl_2 with small amounts of H_2 leads reproducibly to an olefin isomerization-active catalyst. Further optimization allowed for the convenient preparation of the cyclic enol ethers by modifying the ruthenium alkylidene with a 95:5 N_2:H_2 gas mixture.[14] Diluting the H_2 with N_2 affects the desired isomerization while keeping the competing olefin hydrogenation reaction to $\leq 10\%$.

As summarized in Table 1, a series of enol ethers was generated in 46−74% yields in a single reaction vessel from readily prepared dienes.[15] Entries 1, 2, and 6 in Table 1 indicate that five-, six-, and seven-membered cyclic enol ethers can be generated through this ruthenium-catalyzed tandem process. Entries 3−5 suggest that electron-rich and -deficient aromatic substrates, as well as aliphatic dienes, are suitable precursors. As evident in entry 8, tosyl enamides can also be prepared in a manner analogous to that for the enol ethers.[16] Entries 6 and 7 demonstrate that the isomerization can convert the isomeric RCM products to the same seven-membered ring enol ether **14**.



As illustrated in eq 4, the olefin isomerization can proceed through several intermediates to provide the less substituted enol ether **14** from either dienes **13** or **15**. The absence of the more stable enol ether **21** suggests that the isomerization is sensitive to sterics and is unable to generate the trisubstituted enol ether. Several other observations support this conclusion. Attempts to generate enol ether **26** from either diene **22** or **23** were unsuccessful (eq 5);

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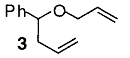
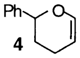
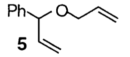
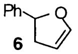
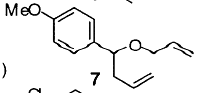
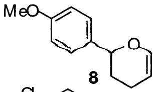
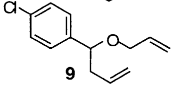
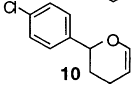
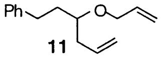
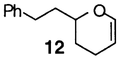
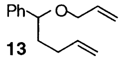
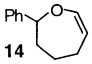
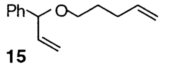
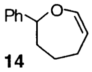
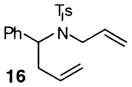
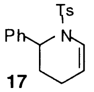
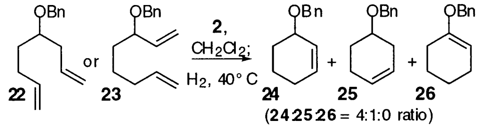
Table 1. Cyclic Enol Ethers through a Tandem Ring-Closing Metathesis−Olefin Isomerization Sequence

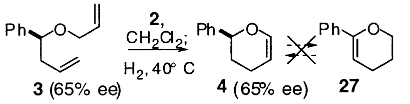
entry	diene	enol ether	yield[a]
(1)	 **3**	 **4**	61%
(2)	 **5**	 **6**	46%
(3)	 **7**	 **8**	65%
(4)	 **9**	 **10**	58%
(5)	 **11**	 **12**	60%
(6)	 **13**	 **14**	54%
(7)	 **15**	 **14**	50%
(8)	 **16**	 **17**	74%

[a] Reaction conditions: 45−70 °C, CH_2Cl_2 [0.03−0.05 M]. Average isolated yield for at least two reactions.

a 4:1 mixture of benzyl ethers **24** and **25** were obtained from either of the diene precursors. In addition, when the enantiomerically enriched diene **3**[17] was subjected to the metathesis−isomerization protocol (eq 6), the resulting enol ether **4** was generated without loss of enantiomeric purity, indicating that the isomerization does not proceed through the achiral enol ether **27**.



22 **23** **24** **25** **26** (**24**:**25**:**26** = 4:1:0 ratio) (eq 5)



3 (65% ee) **4** (65% ee) **27** (eq 6)

The specific ruthenium catalyst responsible for the isomerization is still in question. ^{31}P and ^{1}H NMR studies were inconclusive; treatment of **2** with either H_2 or 95:5 N_2:H_2 on a time scale similar to that used during the reactions (1−3 min) revealed neither a new Ru-hydride, nor an observable change in the ruthenium-alkylidene signal (based on an internal standard). Attempts to "preform" an active Ru-hydride species from **2** by prolonged exposure to H_2 (in the absence of an olefin substrate) revealed a new ^{31}P NMR signal at 48 ppm;[18] however, this pretreatment did not generate an active isomerization catalyst. Nevertheless, with purified alkylidene **2**, only metathesis products are obtained until a small amount of H_2 is introduced into the reaction, suggesting that an active, but yet to be characterized, ruthenium hydride is responsible for the isomerization activity.

In summary, an efficient entry into cyclic enol ethers from readily available starting materials utilizing a tandem RCM−olefin isomerization protocol is presented. Given the notable range of reactions catalyzed by ruthenium complexes, we anticipate this two-step process will represent an early example of tandem sequences utilizing metathesis-active ruthenium alkylidenes. Further studies to determine the specific catalytic species responsible for the olefin isomerization activity, as well as to introduce new ruthenium-catalyzed tandem processes, are underway.

Acknowledgment. Studies on related isomerizations by Alejandro D. Alonso are greatly appreciated. We are grateful to the NSF (CHE-0132221) for financial support. In addition, we thank the Merck Chemistry Council and GlaxoSmithKline for additional funding.

Supporting Information Available: Experimental procedures and data on new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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