ORGANIC LETTERS

2006
Vol. 8, No. 12
2603−2606

Preparation of Aliphatic Ketones through a Ruthenium-Catalyzed Tandem Cross-Metathesis/Allylic Alcohol Isomerization

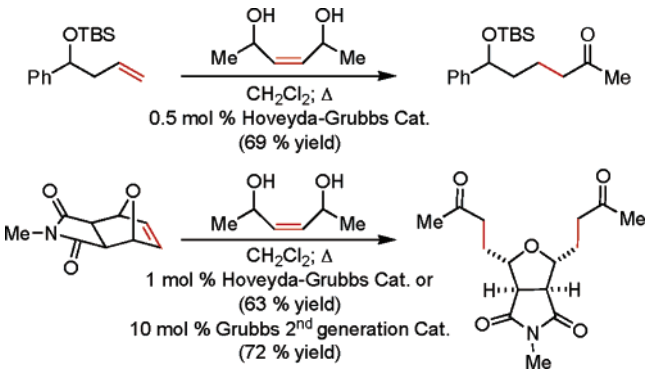
David Finnegan, Benjamin A. Seigal, and Marc L. Snapper*

Department of Chemistry, Merkert Chemistry Center, Boston College, 2609 Beacon Street, Chestnut Hill, Massachusetts 02467

marc.snapper@bc.edu

Received April 14, 2006

ABSTRACT



Grubbs' 2nd generation and Hoveyda–Grubbs' ruthenium alkylidenes are shown to be effective catalysts for cross-metatheses of allylic alcohols with cyclic and acyclic olefins, as well as isomerization of the resulting allylic alcohols to alkyl ketones. The net result of this new tandem methodology is a single-flask process that provides highly functionalized, ketone-containing products from simple allylic alcohol precursors.

Accomplishing several transformations in a single reaction vessel in a controlled and predictable manner can lead to more economical approaches to valuable products. Costs can be reduced if the structural changes that usually require several steps to achieve, in which each step involves time, solvent, reagents, and energy, are realized under a set of compatible reaction conditions in one formal process. Development of new tandem, sequential, cascade, or domino processes provides powerful strategies that help address this objective.[1]

Tandem or concurrent catalysis is a subset of tandem reactions that uses only one catalyst or precatalyst for multiple sequential, but mechanistically distinct transformations.[2] In this report, we describe a tandem catalytic process in which a single ruthenium complex is used to carry out an olefin cross-metathesis and then modified in situ to effect an olefin isomerization in the same reaction vessel. The net

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(2) (a) Bazan, G. C.; Baker, R. T.; Obrey, S. J.; Wasilke, J. C. *Chem. Rev.* **2005**, *105*, 1001. (b) Han, K. D.; Chung, Y. K. *Synlett* **2005**, *12*, 1889. (c) Maier, M. E.; Varseev, G. N. *Org. Lett.* **2005**, *7*, 3881. (d) Pal, M.; Dakarapu, R.; Parasuraman, K.; Subramanian, V.; Yeleswarapu, K. R. *J. Org. Chem.* **2005**, *70*, 7179. (e) Fogg, D. E.; Dos Santos, E. N. *Coord. Chem. Rev.* **2004**, *248*, 2365. For examples that include olefin metatheses, see: (f) Schmidt, B. *Pure Appl. Chem.* **2006**, *78*, 469. (g) Aitken, S. G.; Abell, A. *Aust. J. Chem.* **2005**, 58, 3.

10.1021/ol060918g CCC: $33.50
Published on Web 05/17/2006

result is a unique, single-pot method for converting allylic alcohols into highly functionalized, carbonyl-containing compounds.[3]

The ruthenium catalysts **1**−**3**, shown in Figure 1, have

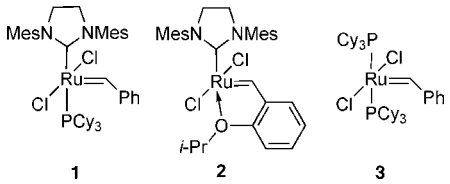
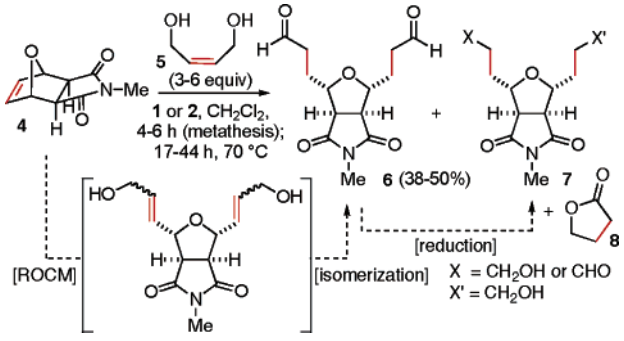


Figure 1. Ruthenium metathesis catalysts.

been employed extensively for olefin metatheses due to their functional-group tolerance and relative ease of handling.[4] Our experience with the synthesis of cyclic enol ethers[5] through a tandem metathesis/isomerization process suggested that saturated carbonyls could be derived from allylic alcohols through a similar isomerization. This idea was supported substantially by several reports demonstrating the isomerization of allylic alcohols to saturated carbonyl compounds[6] with Grubbs' first generation catalyst **3**.[7] Given these observations, we expected cross-metathesis of an allylic alcohol followed by an olefin isomerization would offer a unique and rapid entry into saturated, carbonyl-containing compounds.

Our initial studies employed allyl alcohol or (*Z*)-but-2-ene-1,4-diol (**5**) in ring-opening cross-metatheses (ROCM) with strained, cyclic olefins (Scheme 1). In this case, the

Scheme 1. Ruthenium-Catalyzed Tandem Ring-Opening Cross-Metathesis/Isomerization with (*Z*)-Butene-1,4-diol **5**



isomerization of the primary allylic alcohol was expected to yield aldehyde-containing products. We found that after the ROCM was complete, the ruthenium complex could then be transformed into an effective isomerization catalyst through heating. Our previous work suggested that hydrogen was necessary to effect the isomerization;[8] however, in the presence of allylic alcohols, alternative catalyst "decomposition" pathways are known.[6a] This mechanistic possibility was supported by the observation of a CO absorption (1941 cm^{-1}) in the ruthenium complex recovered after silica gel chromatography,[9] a ligand functionality consistent with Werner's allylic-alcohol mediated decomposition of Grubbs' catalyst.

A persistent problem in these tandem reactions, however, is the variable yields of the desired dialdehyde **6** and the isolation of significant amounts of over-reduced byproducts (**7**). In the case of reactions with diol **5**, the isolation of γ−hydroxybutyrolactone **8** suggested the hydride source. The excess butene-1,4-diol was isomerizing to γ-hydroxybutanal and then undergoing a hydride transfer to form lactone **8** (Scheme 1).[10] This hydride may in fact be the source of the over-reduction problem, as well as the ruthenium hydride deemed responsible for the olefin isomerization reaction. Because the isomerization and reduction occurred with similar efficiencies, stopping the isomerization reaction early did not allow for the isolation of appreciable amounts of the desired aldehyde-containing products. Adjusting temperature and screening additives also failed to provide high yields of the nonreduced products. Given this shortcoming, we decided to work around the over-reduction problem by shifting our focus to the synthesis of ketones.

Reducing the likelihood of hydride transfer by using a secondary allylic alcohol, such as but-3-en-2-ol or (*Z*)-hex-3-ene-2,5-diol (**9**), in the cross-metatheses proved to be a robust method for generating methyl ketone-containing substrates. To avoid oligomerization of the strained olefins (i.e., ROMP) during cross-metathesis with diol **9**, slower addition of the cyclic olefin to the reaction was necessary. Moreover, the isomerization led to the desired diketones in

(3) (a) Gree, R.; Crévisy, C.; Uma, R. *Chem. Rev.* **2003**, *103*, 27. (b) van der Drift, R. C.; Bouwman, E.; Drent, E. *J. Organomet. Chem.* **2002**, *650*, 1.

(4) (a) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, 1, 953. (b) Garber, S. B.; Kingbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168. (c) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2039. For reviews on olefin metatheses, see: (d) Furstner, A. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 3012. (e) Grubbs, R. H.; Trnka, T. M. *Acc. Chem. Res.* **2001**, *34*, 18. For a comparison of Mo- and Ru-catalyzed olefin-metatheses, see; (f) Schrock, R. R.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4592.

(5) (a) Sutton, A. E.; Seigal, B. A.; Finnegan, D. F.; Snapper, M. L. *J. Am. Chem. Soc.* **2002**, *124*, 13390. For related examples from other laboratories, see: (b) Fustero, S.; Sánchez-Roselló, M.; Jiménez, D.; Sanz-Cervera, J. F.; del Pozo, C.; Aceña, J. L. *J. Org. Chem.* **2006**, *71*, 2706. (c) Schmidt, B. *Eur. J. Org. Chem.* **2004**, 1865. (d) Schmidt, B. *J. Org. Chem.* **2004**, *69*, 7672. (e) Schmidt, B. *Eur. J. Org. Chem.* **2003**, 816. (f) Schmidt, B. *Chem. Commun.* **2004**, 742. (g) Schmidt, B. *Eur. J. Org. Chem.* **2004**, 1865. (h) Bressy, C.; Menant, C.; Piva, O. *Synlett* **2005**, 577.

(6) For example, see: (a) Werner, H.; Grunwald, C.; Stuer, W.; Wolf, J. *Organometallics* **2003**, *22*, 1558. (b) Edlin, C. D.; Faulkner, J.; Fengas, D.; Knight, C. K.; Parker, J.; Preece, I.; Quayle, P.; Richards, S. N. *Synlett* **2005**, *572*.

(7) For studies on the decomposition of alkylidene **3**, see: (a) Hoye, T. R.; Zhao, H. *Org. Lett.* **1999**, *1*, 169. (b) Hoye, T. R.; Zhao, H. *Org. Lett.* **1999**, *1*, 1123. (c) Gurjar, M. K.; Yakambram, P. *Tetrahedron Lett.* **2001**, *42*, 3633. For decomposition studies of alkylidene **1**, see: (d) Grubbs, R. H.; Hong, S. H.; Day, M. W. *J. Am. Chem. Soc.* **2004**, *126*, 7414. (e) Grubbs, R. H.; Louie, J. *Organometallics* **2002**, *21*, 2153.

(8) For examples of ruthenium hydride formation through hydrogenation of ruthenium alkylidenes, see: (a) Caulton, K. G.; Olivan, M. *Inorg. Chem.* **1999**, *38*, 566. (b) Fogg, D. E.; Yap, G. P. A.; Drouin, S. D. *Inorg. Chem.* **2000**, *39*, 5412.

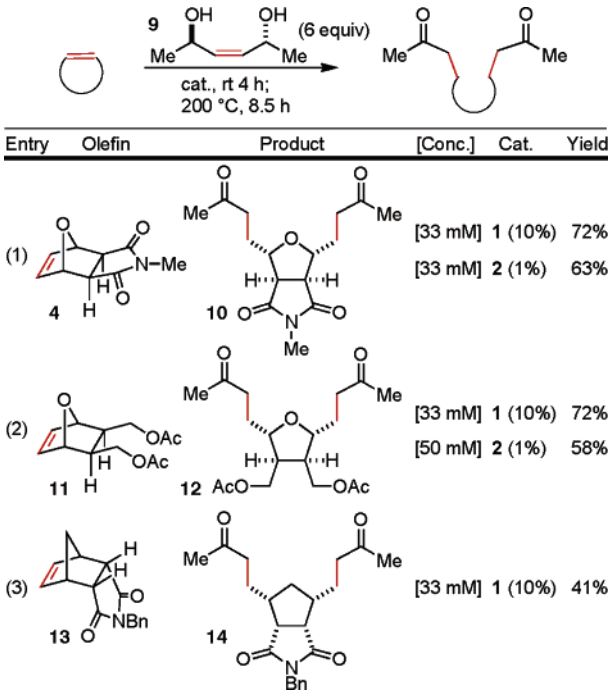
(9) For formation of monometallic ruthenium carbonyls see the reference above, as well as: Moers, F. G.; Ten Hoedt, R. W. M.; Langhout, J. P. *J. Organomet. Chem.* **1974**, *65*, 93.

(10) For a review of similar transformations, see: Huskens, J.; Van Bekkum, H.; Peters, J. A.; De Graauw, C. F. *Synthesis* **1994**, *10*, 1007.

higher yields with shorter reaction times when run at higher temperatures (i.e., 200 °C).

The data summarized in Table 1 show the optimized

Table 1. Tandem Ring-Opening Cross-Metathesis/Isomerization

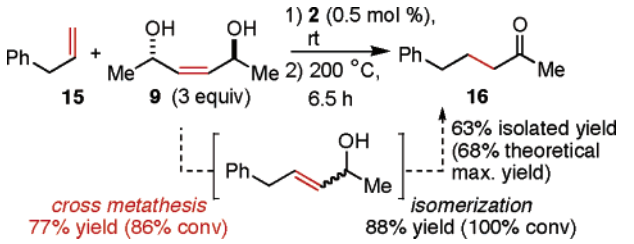


results for tandem ROCM/isomerizations with use of ruthenium complexes **1** and **2**. Entries 1 and 2 demonstrate that 7-oxobicyclo[2.2.1]heptenes (**4** and **11**) are suitable substrates for the tandem ROCM/isomerization. Likewise, entry 3 indicates that the corresponding cyclopentadienyl cycloadduct **13** is also a competent cyclic olefin for this tandem process, albeit with a slightly reduced efficiency. In general, the Hoveyda−Grubbs' alkylidene **2** proved more effective in these reactions, allowing for reduced catalyst loading with only minimal reduction in overall yields.

While the use of strained cyclic olefins is an important feature for driving the ROCM step to completion, we felt that the inclusion of terminal olefins as cross-metathesis (CM) partners would significantly expand the utility of this tandem methodology. Unfortunately, our initial CM/isomerizations were hindered by low conversion in the metathesis step. The observation that the cross-metatheses of allyl benzene with diol **9** with use of ruthenium complex **2** resulted in 90% yield (86% conversion) was useful (Scheme 2). Further optimization of each cross-metathesis allowed for reasonable yields in this tandem CM/isomerization process with relatively low catalyst loading (0.5 to 2 mol %).

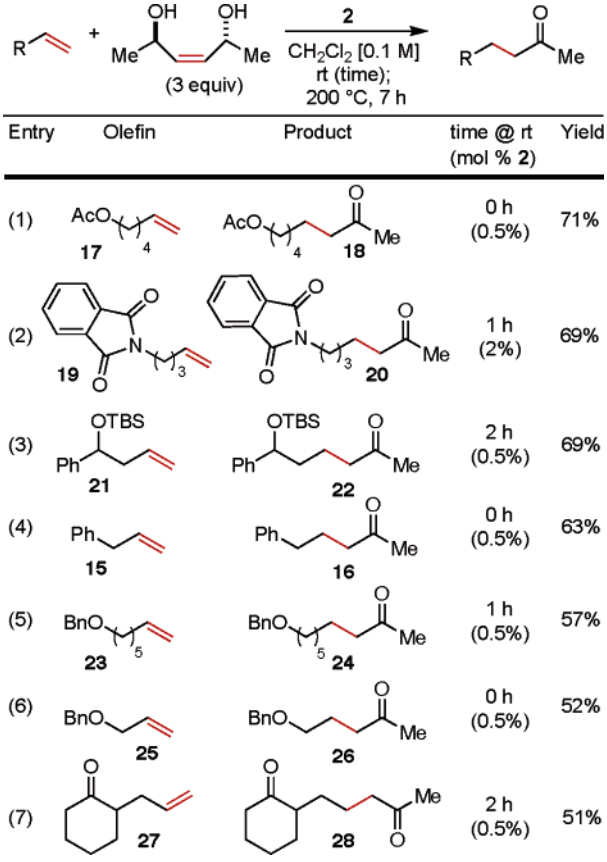
The cross-metathesis/isomerizations of various aliphatic terminal olefins are illustrated in Table 2. The metathesis

Scheme 2. Optimizations of a Tandem, Ruthenium-Catalyzed Cross-Metathesis/Isomerization with (*Z*)-Hex-3-ene-1,4-diol **9**



time was found to be a key substrate-dependent variable in these reactions. The transformation shown in entry 1 indicates that aliphatic acetates (i.e., **17**) are compatible in this tandem process. Phthalimide **19** (entry 2) requires a slightly higher catalyst loading to drive the olefin isomerization step to completion. With lower catalyst loadings, a variety of other olefin isomers was obtained. Entry 3 shows that trialkylsilyl ether **21** is a suitable substrate in this tandem process.[11] The additional metathesis time required for this example is presumably due to the slightly more hindered nature of the terminal olefin. The influence of an aromatic group in close proximity to the olefin is examined in entry 4. In this case, a minor byproduct where the olefin migrated into conjugation with the aromatic ring was isolated in addition to the desired

Table 2. Tandem Cross-Metathesis/Isomerization



(11) Takei, I.; Nishibayashi, Y.; Ishii, Y.; Mizobe, Y.; Uemura, S.; Hidai, M. *J. Organomet. Chem.* **2003**, *679*, 32.

methyl ketone **16**. Entries 5 and 6 illustrate two examples in which the terminal olefins possess benzyl ethers. In either case, ruthenium hydride-mediated hydrogenolysis of the benzyl ethers does not appear to be an issue in these transformations.[12] The example shown in entry 7 demonstrates the chemoselectivity of the tandem process. The preexisting ketone functionality found in substrate **27** does not interfere with the reaction. This observation is useful if the resulting diketone **28** were to be employed in subsequent intramolecular aldol transformations.

In summary, we have developed a new, ruthenium-catalyzed, tandem olefin cross-metathesis/allylic alcohol isomerization protocol that generates methyl ketones[13] from terminal and strained cyclic olefins in a single reaction flask. This advancement extends the utility of the popular ruthenium alkylidenes **1** and **2** by allowing for the direct access of carbonyl functionality through an olefin metathesis-based process.

Acknowledgment. We thank the National Science Foundation and Boston College for financial support. We are grateful to Schering-Plough for X-ray facility support and Materia for the gift of metathesis catalyst.

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

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(12) Bond, G. C.; Hooper, A. D. *Appl. Catal., A* **2000**, *191*, 69.

(13) We anticipate that more functionalized allylic alcohols, if viable substrates in the cross metathesis step, will provide similar access to functionalized ketones through this tandem process.