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Ruthenium-Catalyzed Tandem Olefin Metathesis–Oxidations

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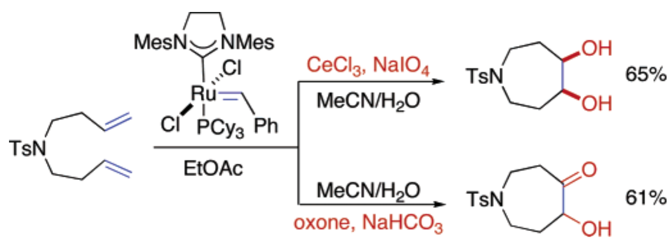
ABSTRACT



The utility of Grubbs' 2nd generation metathesis catalyst has been expanded by the development of two tandem olefin metathesis/oxidation protocols. These ruthenium-catalyzed processes provide *cis*-diols or α-hydroxy ketones from simple olefinic starting materials.

The introduction of well-defined ruthenium complexes, such as **1**−**5** (Figure 1), has helped to establish olefin metathesis as a powerful tool for the construction of carbon−carbon double bonds.[1] These complexes can offer even greater synthetic utility if the metathesis reaction is combined with other ruthenium-catalyzed transformations in the same reaction vessel.[2] The net result can be unique functional group transformations that previously required several independent reactions to accomplish. In this regard, these tandem catalytic processes offer new opportunities for the preparation of complex molecules in a more cost-efficient and environmentally friendly manner. Recent examples of tandem catalysis by metathesis-active ruthenium complexes include olefin metathesis combined with radical atom transfer,[3] olefin isomerization,[4] hydrogenation,[5] and cyclopropanation.[6] Herein, we will describe a tandem, ruthenium-catalyzed olefin metathesis−oxidation sequence for the preparation of *cis*-diols and α-hydroxy ketones from simple olefinic precursors.[7]

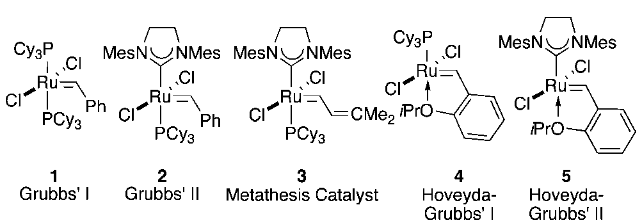


Figure 1. Commercially available metathesis-active ruthenium complexes.

(1) For recent reviews on catalytic olefin metathesis, see: (a) Grubbs, R. H. *Tetrahedron* **2004**, *60*, 7117. (b) Furstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3013. (c) Astruc, D. *New. J. Chem.* **2005**, *29*, 42. (d) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199. (e) Diver, S. T.; Giessert, A. J. *Chem. Rev.* **2004**, *104*, 1317. (e) Mori, M. *J. Mol. Catal. A: Chem.* **2004**, *213*, 73.

(2) For recent reviews on tandem catalysis, see: (a) Fogg, D. E.; dos Santos, E. N. *Coord. Chem. Rev.* **2004**, *248*, 2365. (b) Wasilke, J. C.; Obrey, S. J.; Baker, R. T.; Bazan, G. C. *Chem. Rev.* **2005**, *105*, 1001. (c) Schmidt, B. *Pure Appl. Chem.* **2006**, *78*, 469.

(3) (a) Seigal, B. A.; Fajardo, C.; Snapper, M. L. *J. Am. Chem. Soc.* **2005**, *127*, 16329. (b) Schmidt, B.; Pohler, M. *J. Organomet. Chem.* **2005**, *690*, 5552.

(4) (a) Schmidt, B. *Eur. J. Org. Chem.* **2003**, 816. (b) Schmidt, B. *Chem. Commun.* **2004**, 742. (c) Schmidt, B. *J. Org. Chem.* **2004**, *69*, 7672. (d) Sutton, A. E.; Seigal, B. A.; Finnegan, D. F.; Snapper, M. L. *J. Am. Chem. Soc.* **2002**, *124*, 13390. (e) Finnegan, D.; Seigal, B. A.; Snapper, M. L. *Org. Lett.* **2006**, *8*, 2603.

(5) (a) Furstner, A.; Leitner, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 308. (b) Louie, J.; Bielawski, C. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 11312.

(6) Kim, B. G.; Snapper, M. L. *J. Am. Chem. Soc.* **2006**, *128*, 52.

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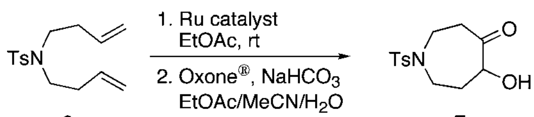
Recently, Plietker and co-workers described $RuCl_3$-catalyzed oxidations of olefins to generate *cis*-diols or α-hydroxy ketones depending on the reaction conditions used. In situ formation of the oxidative species, RuO_4, using $NaIO_4$ and a Lewis[8] or Brønsted acid[9] afforded diols in high yield, whereas treatment with Oxone and $NaHCO_3$ provided α-hydroxy ketones.[10] In light of this useful transformation, we envisioned that it should be possible to modify a ruthenium alkylidene in situ to effect similar oxidations after completing a metathesis reaction.

Initially, we examined the ability of ruthenium alkylidenes **1**−**5** to catalyze the tandem ring-closing metathesis (RCM)/α-ketohydroxylation reaction sequence. On the basis of Plietker's observations, the ketohydroxylation was performed in a 6:6:1 mixture of MeCN/EtOAc/H_2O in the presence of Oxone, $NaHCO_3$, and 5 mol % of the ruthenium catalysts. As indicated in Table 1, the best results were found when alkylidene **2** was employed as the ruthenium source. Further optimization showed that increasing the catalyst loading of **2** to 10 mol % improved the yield slightly to 65% for the tandem process (Table 1, entry 6).

Table 1. Ruthenium Catalysts for α-Ketohydroxylation

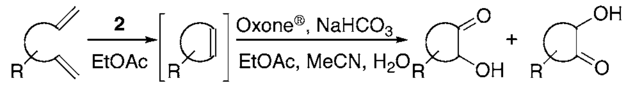


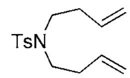
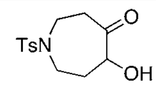
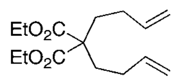
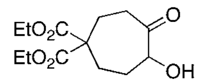
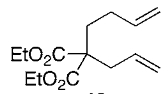
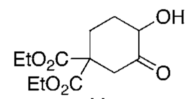
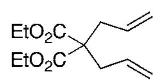
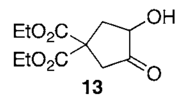
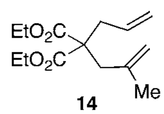
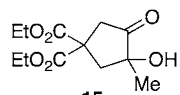
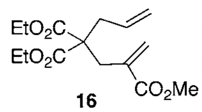
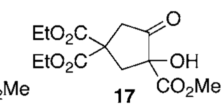
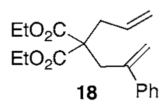
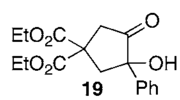
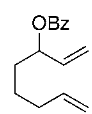
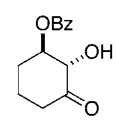
entry	catalyst	time (RCM; oxidation)	yield
(1)	**1**[a]	3 h; 2 h	22%
(2)	**2**[a]	1 h; 10 min	61%
(3)	**3**[a]	3 h; 10 min	40%
(4)	**4**[a]	1 h; 10 min	45%
(5)	**5**[a]	1 h; 10 min	45%
(6)	**2**[b]	1 h; 10 min	65%

[a] Conditions: Ru catalyst (5 mol %), rt, [0.1−0.2 M in EtOAc]; $NaHCO_3$, Oxone, MeCN/H_2O (6:1). [b] Conditions: Ru catalyst (10 mol %), rt, [0.1−0.2 M in EtOAc]; $NaHCO_3$, Oxone, MeCN/H_2O (6:1).

Following these observations, the RCM/α-ketohydroxylation of other olefinic substrates was studied; these results are reported in Table 2. When the dienes were treated with 5 mol % of Grubbs' 2nd generation catalyst **2** in ethyl acetate, the RCM was complete within 1 h. The reactions were then diluted with MeCN/H_2O and treated with $NaHCO_3$ and Oxone. The oxidation was rapid (∼10−20 min) and provided the α-ketohydroxylated products in 42−61% overall yields. It was observed that the oxidation of unsymmetrical substrates led to a mixture of regioisomers; for example, the α-ketohydroxylations shown in entries 3 and 8 of Table 2 occur with only 2:1 regioselectivity (major product shown). As described in entry 8, however, the reaction can proceed with high diastereoselectivity when a stereocenter is proximal to the olefin (only one diastereomer observed by ^1H NMR for the major regioisomer). Finally, oxidations of trisubstituted olefins, such as in entries 5−7 (Table 2), lead selectively to the corresponding tertiary alcohol-containing products in 42−53% yields.

Table 2. Tandem Ring-Closing Metathesis/α-Ketohydroxylation



entry	diene	product	yield (regioselectivity)
(1)	 **6**	 **7**	61%[a]
(2)	 **8**	 **9**	60%[a]
(3)	 **10**	 **11**	51%[a] (2:1)
(4)	 **12**	 **13**	46%[a]
(5)	 **14**	 **15**	51%[b]
(6)	 **16**	 **17**	53%[b]
(7)	 **18**	 **19**	42%[b]
(8)	 **20**	 **21**	60%[a] (2:1)

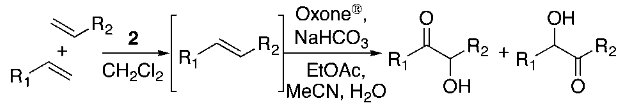
[a] Conditions: **2** (5 mol %), rt, [0.1−0.2 M in EtOAc]; $NaHCO_3$, Oxone, MeCN/H_2O (6:1). [b] Conditions: **2** (10 mol %), rt, [0.1−0.2 M in EtOAc]; $NaHCO_3$, Oxone, MeCN/H_2O (6:1).

Given the success of the tandem RCM/α-ketohydroxylation sequence, the strategy was expanded to include cross-metatheses (CM). Initial olefinic reaction partners were chosen to afford the corresponding CM products in good yield and *E*/*Z* selectivity.[11] Screening of the CM conditions indicated that performing the metathesis in CH_2Cl_2 with a

(7) For a similar contribution, see: Beligny, S.; Eibauer, S.; Maechling, S.; Blechert, S. *Angew. Chem., Int. Ed.* **2006**, *45*, 1900.
(8) Plietker, B.; Niggemann, M. *J. Org. Chem.* **2005**, *70*, 2402.
(9) Plietker, B.; Niggemann, M. *Org. Lett.* **2003**, *5*, 3353.
(10) (a) Plietker, B. *J. Org. Chem.* **2003**, *68*, 7123. (b) Plietker, B. *J. Org. Chem.* **2004**, *69*, 8287. (c) Plietker, B. *Eur. J. Org. Chem.* **2005**, 1919.

1:2 mixture of olefins gave the desired CM products in excellent yield. For the ketohydroxylation step, the excess cross-metathesis partner and solvent were removed in vacuo prior to addition of the oxidants. The results of this study are summarized in Table 3. The yields for the tandem process

Table 3. Tandem Cross-Metathesis/α-Ketohydroxylation[a]



entry	olefin 1	olefin 2 (2 equiv)	product	yield (regioselectivity)
(1)	**22**	**23**	**24**	66% (1:1)
(2)	**25**	**23**	**26**	56% (1.5:1)
(3)	**27**	**23**	**28**	56% (2:1)
(4)	**22**	**29**	**30**	49%
(5)	**25**	**29**	**31**	76%
(6)	**27**	**32**	**33**	47%

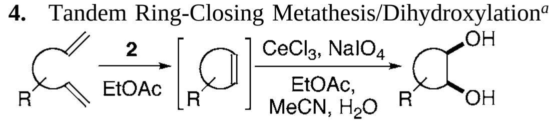
[a] Conditions: **2** (10 mol %), rt, [0.1−0.2 M in CH_2Cl_2]; $NaHCO_3$, Oxone, EtOAc/MeCN/H_2O (6:6:1).

ranged from 49 to 76%, and like the RCM examples, the regioselectivity of the oxidation was generally low. It was proposed that the mixtures observed were due to a selective oxidation followed by an isomerization of the resulting *β*-keto esters under the reaction conditions. This supposition was supported by a control experiment, where purified *β*-keto ester **24** was shown to equilibrate to the corresponding regioisomer under the basic oxidation conditions.[12] On the other hand, entries 4 and 5 of Table 3 indicate that cross-metatheses with methyl methacrylate, which lead to a trisubstituted olefin, afford the α-hydroxy ketone products with high selectivity. Entry 6 illustrates that the tandem cross-metathesis/oxidation of *cis*-1,4-dichloro-2-butene (**32**) with styrene (**27**) provided selectively ketohydroxy isomer **33**.

Plietker and co-workers have also recently described a $RuCl_3$-catalyzed dihydroxylation of olefins.[8] In this report, the treatment of an olefin with $RuCl_3$ and $NaIO_4$ in the presence of either a Brønsted or Lewis acid provided the desired *cis*-diols in good yield. Given this observation, a tandem olefin-metathesis/dihydroxylation was investigated as a further extension of this methodology. Recently, Blechert and co-workers reported a similar finding.[7] In our case, however, the method was made more practical by eliminating the need to change solvents and, for several examples, provided the diol products with improved yields.

On the basis of our results from the metathesis/α-ketohydroxylation studies, optimization of the metathesis/dihydroxylation conditions was performed with alkylidene **2**. After completion of the RCM step, the EtOAc solution containing the metathesis products was added to a stirred suspension of the preformed Ce(IV)−periodato complex in a 6:1 mixture of MeCN/H_2O. This complex was formed by the treatment of 1.5 equiv of $NaIO_4$ with 10 mol % of $CeCl_3$·$7H_2O$. It was observed that the reaction was rapid (∼10−20 min) and provided the desired *cis*-dihydroxylated products in 63−81% yields (Table 4). Control experiments showed

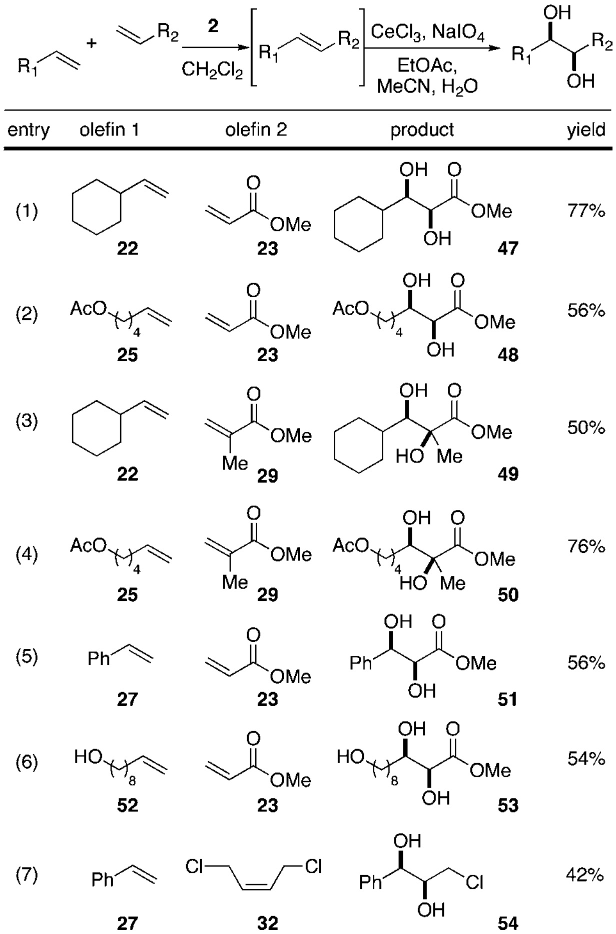
Table 4. Tandem Ring-Closing Metathesis/Dihydroxylation[a]



entry	diene	product	yield (regioselectivity)
(1)	**34**	**35**	63%
(2)	**36**	**37**	69%
(3)	**6**	**38**	65%
(4)	**8**	**39**	67%
(5)	**40**	**41**	60% (22:1)
(6)	**20**	**42**	81%
(7)	**43**	**44**	69% (3:2)
(8)	**45**	**46**	77% (7:1)

[a] Conditions: **2** (5 mol %), rt, [0.1−0.2 M in EtOAc]; $NaIO_4$, $CeCl_3$·$7H_2O$, MeCN/H_2O (6:1).

Table 5. Tandem Cross-Metathesis/Dihydroxylation



[a] Conditions: **2** (5 mol %), rt, [0.1−0.2 M in CH_2Cl_2]; $NaIO_4$, $CeCl_3 \cdot 7H_2O$, EtOAc/MeCN/H_2O (6:6:1).

that the oxidation does not proceed in the absence of the ruthenium complex.

As the data presented in Table 4 indicate, a variety of functional groups can be tolerated in this tandem sequence. Entries 1−4 of Table 4 illustrate that five-, six-, and seven-membered cyclic diols can be accessed in ≥63% yield. As represented by the results shown in entries 5 and 6, the reaction also displays high diastereoselectivity when a nearby stereocenter is present. With more remote stereogenic centers, the diastereoselectivity of the dihydroxylation is reduced (3:2 for entry 7 and 7:1 for entry 8, Table 4). The relative stereochemical assignments of the dihydroxylated compounds were determined by nOe studies on the corresponding acetonide derivatives.

The tandem olefin metathesis/dihydroxylation was also extended to include cross-metatheses. The data in Table 5 demonstrate that a variety of functional groups including aliphatic and aromatic olefins are viable substrates for the tandem CM/dihydroxylation reaction sequence. The CM step of the tandem process can be performed in a variety of solvents. For example, reaction of vinylcyclohexane (**22**) and methylacrylate (**23**) in EtOAc gives diol **47** in 49% isolated yield; in CH_2Cl_2, the diol is isolated in 77% yield, and when the reaction is run in the absence of solvent, the diol is isolated in 19% yield. These reactions could be made even more operationally simple, therefore, by performing the metathesis reaction in EtOAc instead of in CH_2Cl_2.[13] As was the case with the ketohydroxylations, trisubstituted olefins are acceptable in the dihydroxylation step. Entries 3 and 4 in Table 5, for example, indicate the formation of these more hindered diols in 50% and 76% yields, respectively.

In summary, two new ruthenium-catalyzed tandem transformations for the generation of α-hydroxy ketones and *cis*-diols have been developed. Owing to its ease of use, this methodology will allow access to important oxygenated intermediates in a more cost-effective and environmentally friendly manner. Additional studies to extend further the scope and utility of these tandem transformations are underway.

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

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(11) Chatterjee, A. K.; Choi, T. L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360.

(12) See Supporting Information for experimental details.

(13) For an example of an olefin metathesis using EtOAc as solvent, see: Evans, P.; Grigg, R.; Monteith, M. *Tetrahedron Lett.* **1999**, *40*, 5247.