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# Investigations of the Scope and Mechanism of the Tandem Hydroesterification/Lactonization Reaction

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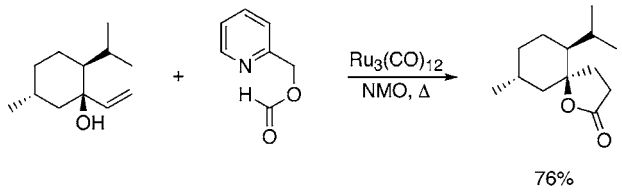
## ABSTRACT




**Heating allylic and homoallylic alcohols and 2-pyridylmethyl formate in the presence of $Ru_3(CO)_{12}$ initiates a tandem sequence of hydroesterification and lactonization. Mechanistic studies suggest that regioselectivity and overall reaction efficiency are governed by the relative rates of reductive elimination and $\beta$-hydride elimination for the alkylruthenium intermediates.**

Processes that couple alkene hydrometalation and reductive elimination provide an attractive approach for homologating and functionalizing olefins.[1] Forming the requisite metal hydrides through carbon−hydrogen bond activation[2] is a particularly desirable aspect of this process with respect to operational simplicity and reagent accessibility. We became interested in this reaction class through our application of Chang's ruthenium-catalyzed olefin hydroesterification reaction[3] in the context of synthetic efforts[4] toward the naturally occurring HIV integrase inhibitor integramycin.[5] In this process we converted an enantiomerically pure homoallylic alcohol into a $\delta$-lactone (Figure 1) in a single operation by heating with $Ru_3(CO)_{12}$ in 2-pyridylmethyl formate. This tandem hydroesterification/lactonization sequence is significant in that it is a rare example of an intermolecular process of this type proceeding with the alkene component as the limiting reagent. An unexpected outcome in this study was the isolation of a significant amount of the $\gamma$-lactone that forms from the branched hydroesterification product. This result contrasts with Chang's demonstration that allylic substitution results in excellent selectivity for linear hydroesterification products and indicates that the free hydroxyl

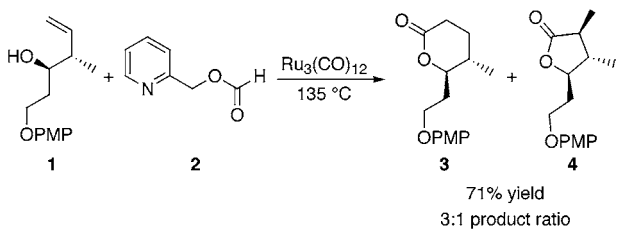



**Figure 1.** Lactone formation through hydroesterification.

(1) For recent examples, see: (a) Willis, M. C.; McNally, S. J.; Beswick, P. J. *Angew. Chem., Int. Ed.* **2004**, *43*, 340. (b) Jun, C.-H.; Moon, C. W.; Lee, D.-Y. *Chem. Eur. J.* **2002**, *8*, 2423. (c) Wiedemann, S. H.; Bergman, R. G.; Ellman, J. E. *Org. Lett.* **2004**, *6*, 1685. (d) DeBoef, B.; Pastine, S. J.; Sames, D. *J. Am. Chem. Soc.* **2004**, *126*, 6556.

(2) (a) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731. (b) Labinger, J. A.; Bercaw, J. E. *Nature* **2002**, *147*, 507. (c) Dyker, G. *Angew. Chem., Int. Ed.* **1999**, *38*, 1699.

(3) Ko, S.; Na, Y.; Chang, S. *J. Am. Chem. Soc.* **2002**, *124*, 750.

(4) Wang, L.; Floreancig, P. E. *Org. Lett.* **2004**, *6*, 569.

(5) Singh, S. B.; Zink, D. L.; Heimbach, B.; Genilloud, O.; Teran, A.; Silverman, K. C.; Lingham, R. B.; Felock, P.; Hazuda, D. C. *Org. Lett.* **2002**, *4*, 1123.

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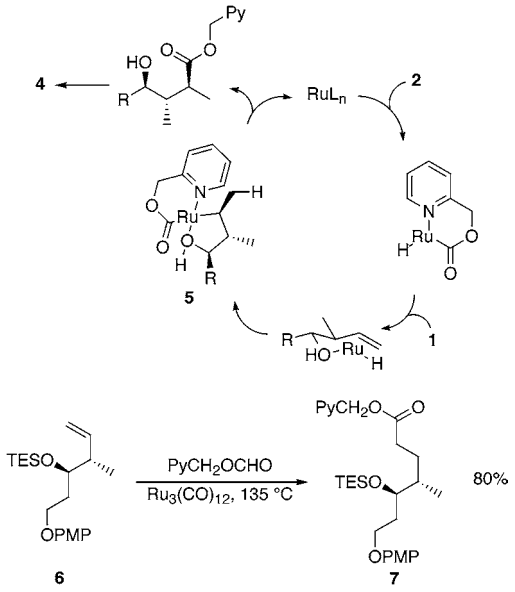



**Figure 2.** Promotion and suppression of branched product formation.

group plays a role in determining the regiochemical outcome of the reaction. In this Letter we report our studies directed toward determining the scope of this process and understanding the function of the hydroxyl group through constructing a structure−reactivity relationship and through the use of deuterated pyridylmethyl formate as a mechanistic probe.

Our initial proposal for branched product formation invoked hydroxyl coordination in the hydrometalation step (Figure 2) to lower the barrier of formation for the secondary alkylruthenium species **5**. This mechanism presupposes that product selectivity is determined by hydrometalation regiochemistry and is consistent with our observation that branched product formation is eliminated by suppressing hydroxyl group coordination through silyl ether formation. Silyl-protected substrates can also engage in a one-pot hydroesterification/lactonization reaction by adding HOAc upon completion of ester formation.

Promoting heteroatom complexation requires an open coordination site on ruthenium. Although the exact nature of the catalyst in this process has yet to be determined, clearly extensive ligand loss from the coordinatively saturated $Ru_3(CO)_{12}$ must precede C−H insertion and olefin binding. Inspired by Schreiber's studies[6] on the Pauson−Khand reaction, we added *N*-methylmorpholine *N*-oxide (NMO) to the reaction mixture to open coordination sites by sequestering and oxidizing transiently dissociated CO. Adding 5−15 mol % NMO resulted in a rate enhancement at 135 °C and allowed us to lower the reaction temperature from 135 to 95 °C, a temperature at which no reaction was observed under the original protocol. In addition to providing less thermally demanding reaction conditions, this change permitted us to conduct subsequent mechanistic studies at two temperatures and to enhance reaction rates for sterically hindered substrates at 135 °C.

(6) Shambayati, S.; Crowe, W. E.; Schreiber, S. L. *Tetrahedron Lett.* **1990**, *31*, 5289.

**Table 1.** Hydroesterification of Functionalized Olefins[a]

| entry | substrate[b] | products (yield) | |
|---|---|---|---|
| 1 | **8** | **9** (48%)[c] | **10** (25%) |
| 2 | **11** | **12** (28%) | **13** (9%) |
| | | **14** (33%) | |
| 3 | **15** | **16** (40%) | **17** (28%) |
| 4 | **18** | **19** (78%) | **17** (5%) |
| 5 | **20** | **21** (72%)[c,d] | |
| 6 | **22** | **23** (65%) | **24** (35%) |
| 7 | **25** | **26** (76%) | |
| 8 | **27** | **28** (37%) | **29** (21%) |
| | | **30** (19%) | **31** (20%) |

[a] General procedure: substrate, $Ru_3(CO)_{12}$ (5 mol %), and NMO (5−15 mol %) were stirred at 100−135 °C in pyridylmethyl formate for 1.5−12 h. HOAc was added to complete lactonization when necessary. [b] R = *n*-hexyl. [c] Isolated as a 1:1 mixture of diastereomers. [d] Yield at 89% conversion.

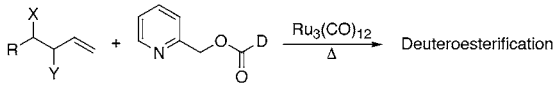
To gauge the scope of this reaction with functionalized olefins as limiting reagents and to assess the potential of hydroxyl coordination to alter the regiochemical outcome of the hydroesterification reaction, we prepared several substrates and exposed them to hydroesterification conditions (Table 1). Homoallylic alcohol **8**, in which the absence of branching at the allylic carbon was expected to be less detrimental to the formation of the branched product relative to previous substrates, indeed provided $\gamma$-lactone **9** (48%) as a diastereomeric mixture and $\delta$-lactone **10** (25%). This result, while not immediately useful in a synthetic sense,

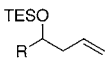
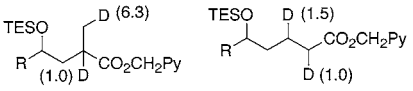
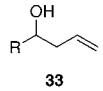
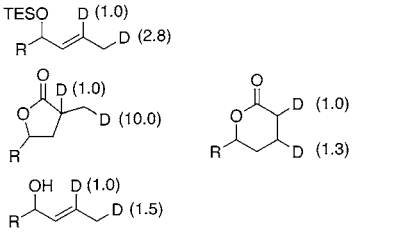
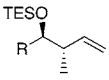
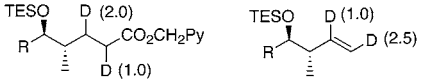
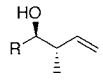
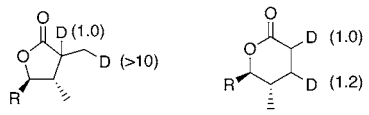
demonstrates that coordination has the capacity to reverse the regiochemical outcome of hydroesterification reactions. As expected, hydroesterification of silyl ether **11** provided a mixture of linear ester **12** and branched ester **13** in an approximately 3:1 ratio. The major product in this reaction, however, was olefin isomer **14**. Allylic alcohol **15** provided only a moderate yield of $\gamma$-lactone **16**, with the major side product resulting from starting material isomerization to form ketone **17**. Isomerization can be suppressed by silylation of the hydroxyl group. Ether **18** underwent hydroesterification to yield ester **19** in good yield, ultimately providing an excellent method for $\gamma$-lactone formation from allylic alcohols. Internal olefins proved to be much less reactive than terminal olefins (data not shown), but 1,1-disubstituted alkene **20** reacted efficiently, albeit slowly, to form lactone **21** as a 1:1 mixture of diastereomers. Hindered neopentyl and tertiary alcohols proved to be very suitable substrates. Disubstitution at the allylic position (entry 6) actually resulted in quantitative hydroesterification, though the linear to branched ratio was only approximately 2:1. Notably, menthone derivatives **25** and **27**, which were poor substrates for a recently reported[7] metathesis-based lactonization strategy, were converted to spirocyclic lactones **26** and **29**[8] in satisfactory yields. Hindered substrates reacted most efficiently in sealed tubes, most likely because the substrates are somewhat volatile and can be lost upon prolonged heating.

The formation of ketone **17** and varying amounts of olefin isomers of the starting materials suggest that $\beta$-hydride elimination can be competitive with reductive elimination, thereby challenging our original hypothesis of product selectivity being set in the hydrometalation step. To obtain a more precise understanding of the reaction mechanism, we initiated a study in which deuterated pyridylmethyl formate, easily prepared from commercially available $DCO_2D$, served as a deuterioesterification reagent.[9] In these experiments we define α-deuteration as deuterium incorporation on the carbon bearing the ester group and $\beta$-deuteration as deuterium incorporation on the adjacent carbon. Exclusive $\beta$-deuteration would be expected if product regiochemistry were solely dictated by the initial hydrometalation step, whereas a mixture of α- and $\beta$-deuteration would be expected if hydrometalation were reversible. The site of deuterium incorporation is readily monitored by deuterium NMR. We subjected **32**−**35** to deuterioesterification conditions. The results of this study are shown in Table 2.

A striking observation from this work is that little or no selectivity is observed in the site of deuterium incorporation in most of the reaction products. Also noteworthy is that stopping the hydroesterification of **34** prior to complete conversion resulted in the isolation of starting material in which deuterium was incorporated at both vinylic positions.

**Table 2.** Deuterium Incorporation Studies[a]




| entry | substrate[b] | products (deuteration ratio) |
|---|---|---|
| 1 |  **32** |  |
| 2[c] |  **33** |  |
| 3 |  **34** |  |
| 4 |  **35** |  |

[a] General procedure: substrate, $Ru_3(CO)_{12}$ (5 mol %), and NMO (5−15 mol %) were stirred at 100−135 °C in deuterated pyridylmethyl formate for 1.5−12 h. [b] R = *p*-methoxyphenoxyethyl. [c] Reaction conducted at 100 °C.

These results strongly indicate that hydrometalation is reversible and that regiochemical preferences in this step cannot be the sole determinant in the partitioning between linear and branched products for this series of compounds.

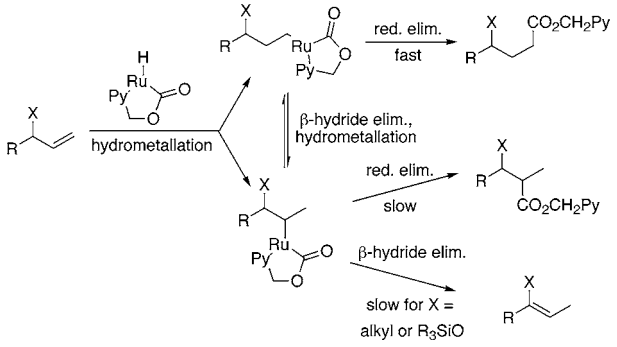



**Figure 3.** Mechanistic pathways for hydroesterification.

Figure 3 shows a revised mechanism that is consistent with the deuteration patterns shown in Table 2. Hydrometalation proceeds with no selectivity, even with substrates that are branched at the allylic position. $\beta$-Hydride elimination is, in most cases, rapid relative to reductive elimination. Internal olefin formation by $\beta$-hydride elimination accounts for

(7) Cossy, J.; Baraggia, F.; BouzBouz, S. *Org. Lett.* **2003**, *5*, 459.

(8) Although ester **28** cyclized only reluctantly under thermal conditions, it can be converted to lactone **29** quantitatively by treatment with NaH in THF. See Supporting Information for details.

(9) For related examples of using deuteration as a mechanistic probe in hydrometalation reactions, see: (a) Casey, C. P.; Martins, S. C.; Fagan, M. A. *J. Am. Chem. Soc*. **2004**, *126*, 5585. (b) Bosnich, B. *Acc. Chem. Res.* **1998**, *31*, 667. (c) Evans, D. A.; Fu, G. C.; Anderson, B. A. *J. Am. Chem. Soc.* **1992**, *114*, 6679.

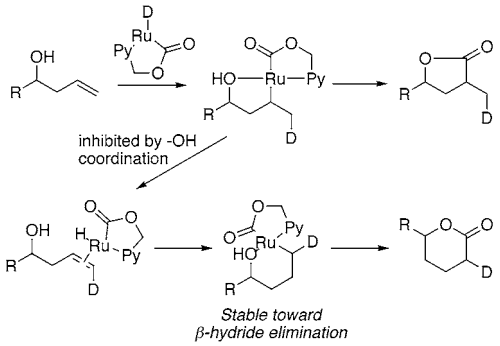



**Figure 4.** Role of coordination in hydroesterification.

starting material isomerization. As discussed above, these products undergo hydroesterification reactions only very slowly under our conditions. Allylic branching suppresses starting material isomerization, leading to enhanced efficiency for ester formation for all substrates except allylic alcohols. The selectivity for linear products thus arises from reductive elimination being more efficient for primary alkylruthenium species than for secondary species, either through having an inherently lower energy of activation or through $\beta$-hydride elimination being significantly faster for secondary alkylruthenium compounds. Branching provides further drive for linear product formation. This can be attributed to steric hindrance disfavoring the branched isomer as the alkylruthenium intermediates equlibrate prior to $\beta$-hydride elimination.

The conspicuous diminution of α-deuteration in the branched products of entries 2 and 4 provides compelling evidence for the role of heteroatom coordination (Figure 4). These data indicate that the primary alkylruthenium species undergoes reductive elimination in nearly exclusive preference to $\beta$-hydride elimination. This result is most economically ascribed to the hydroxyl group occupying the coordination site that is required for $\beta$-hydride elimination. By analogy, coordination must slow $\beta$-hydride elimination to a sufficient extent in branched intermediates for reductive elimination to become a competitive pathway.[10] Although this analysis explains improved efficiency for branched product formation, it does not explain its *preference* from **8**. In this reaction we postulate that branched hydrometalation is favored over linear hydrometalation, possibly resulting from hydroxyl coordination, thereby increasing the concentration of the secondary alkylruthenium species and promoting branched product formation.

We have demonstrated that hydroesterification reactions of functionalized olefins can proceed efficiently even when the olefin is used as the limiting reagent. These processes proceed most effectively when branching is present at the allylic position to suppress olefin isomerization and can be conducted on 100 mmol scale.[11] Homoallylic hydroxyl groups promote the formation of branched esters to a modest extent. Mechanistic studies with deuterated pyridylmethyl formate show that, whereas the hydroxyl group might very well influence the regiochemistry of the hydrometalation step, the partitioning of products between linear and branched isomers is dependent upon the relative rates of reductive elimination between primary and secondary alkylruthenium species. The hydroxyl group serves to slow $\beta$-hydride elimination of the secondary alkylruthenium species to an extent that allows reductive elimination to be a viable process.

Application of hydrometalation/reductive elimination processes to complex molecule synthesis will ultimately require an understanding of the effects of remote functionality on regiochemistry and efficiency. Elucidating the consequences of heteroatom coordination through mechanistic studies of the type described herein will prove to be beneficial in the design of procedural variants that expand the scope of this useful reaction class.

**Acknowledgment.** This work was supported by generous funding from the National Science Foundation.

**Supporting Information Available:** Full experimental procedures and characterization data for all new compounds and deuterium NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) For a discussion on the roles of coordination in reductive elimination and $\beta$-hydride elimination, see: Collman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. *Principles and Applications of Organotransition Metal Chemistry*; University Science Books: Mill Valley, CA, 1987.

(11) Seiders, J. R., II. Unpublished results.