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Tandem Cross-Metathesis/Hydrogenation/Cyclization Reactions by Using Compatible Catalysts

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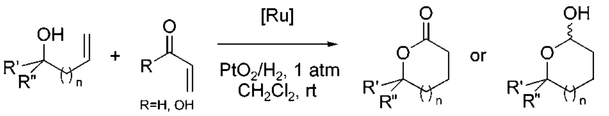
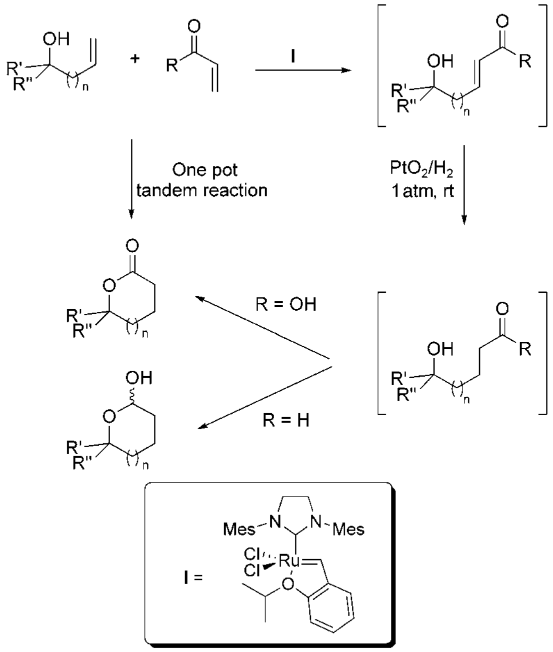
ABSTRACT



A one-pot tandem cross-metathesis/hydrogenation/cyclization procedure was achieved at room temperature, under 1 atm of hydrogen, in the presence of a ruthenium catalyst and PtO_2 showing the compatibility of the two catalysts. This tandem reaction allows the synthesis of substituted lactones and lactols from acrylic acid and acrolein, respectively, in the presence of unsaturated alcohols.

One of the challenging goals of synthetic chemistry is the development of new reactions and strategies that allow for the facile conversion of simple compounds into complex molecules. In this regard, the use of homogeneous transition-metal catalysts has been successful.[1] Organometallic catalysts are traditionally designed and optimized to mediate a single reaction. The increasing demand for efficient synthetic processes requires the development of organometallic reagents that are capable of catalyzing multiple reactions or are compatible with other catalysts to perform sequential reactions. For example, the second generation ruthenium Grubbs' catalyst is able to catalyze a tandem ring-closing metathesis (RCM)/hydrogenation reaction under a hydrogen atmosphere.[2] However, the in situ alignment of several distinct catalytic processes, which is quite common in enzyme-catalyzed reaction sequences,[3] is still at an early stage in homogeneous transition-metal catalysis.[4]

Scheme 1



In a recent paper, we have described a one-pot tandem cross-metathesis/hydrogenation process and shown the compatibility of ruthenium catalyst **I**[5,6] (Scheme 1) with PtO_2[5] under 1 atm of hydrogen, which produced linear γ-silylated functionalized compounds.[7] Herein, we would like to report a three-step one-pot synthesis of cyclic compounds such as

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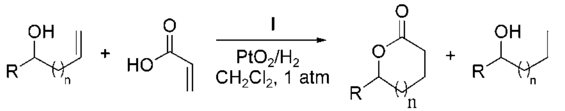
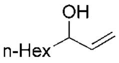
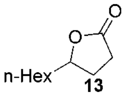
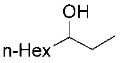
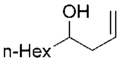
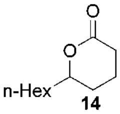
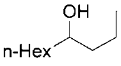
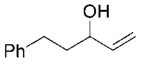
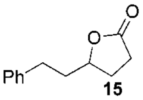
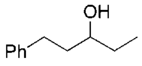
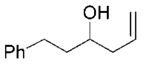
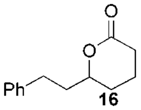
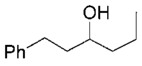
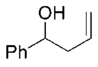
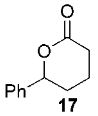
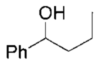
(1) Tsuji, J. *Transition Metal Reagent and Catalyst*; Wiley & Sons: Susex, UK, 2000. (b) Beller, M.; Bolm, C. *Transition Metals for Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 1998.

(2) Louie, J.; Bielawski, C. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 11312−11313. (b) Børsting, P.; Nielsen, P. *J. Chem. Soc., Chem. Commun.* **2002**, 2140−2141.

10.1021/ol027347m CCC: $25.00

Table 1. Lactones from Secondary Unsaturated Alcohols

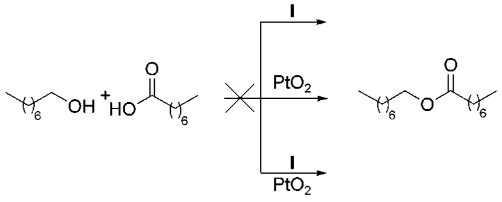


Entry	Unsaturated alcohol	Lactone (yield %)[a]	Saturated alcohol (yield %)[b]
1	 **1**	 **13** (45)	 **1'** (-)
2	 **2**	 **14** (66)	 **2'** (-)
3	 **3**	 **15** (70)	 **3'** (-)
4	 **4**	 **16** (50)	 **4'** (-)
5	 **5**	 **17** (10)	 **5'** (-)

[a] Isolated yields. [b] Not detected by GC/MS.

substituted lactones and lactols. We choose to synthesize substituted lactones and lactols since most of the synthetic methods to access these compounds require several steps.[8] Scheme 1 shows the synthetic pathway to these products from allylic and homoallylic alcohols.

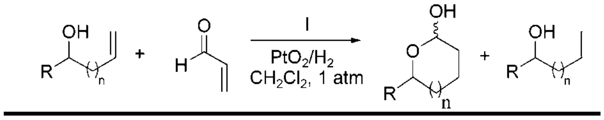
Scheme 2

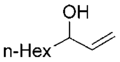
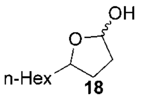
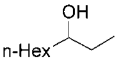
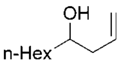
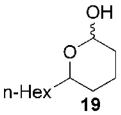
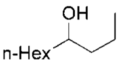
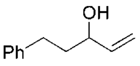
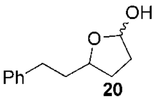
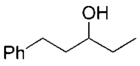
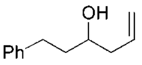
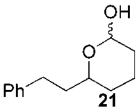
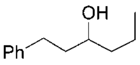
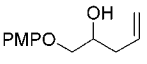
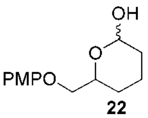
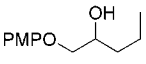


The first step was accomplished by using ruthenium catalyst **I**, and the second step, which involved a hydrogenation, was achieved in the presence of PtO_2. The cyclization took place in situ after the formation of the ω-hydroxy acids or ω-hydroxy aldehydes. As expected, ruthenium catalyst **I** was tolerant of all the reaction conditions and effective for the first reaction. Thus, lactones and lactols were prepared from readily available chemicals in a three-step one-pot reaction.

Treatment of allylic or homoallylic alcohols (1.0 equiv) with acrylic acid (3.0 equiv) in CH_2Cl_2 at room temperature in the presence of ruthenium catalyst **I** (0.05 equiv) and PtO_2

Table 2. Lactols from Secondary Unsaturated Alcohols



Entry	Unsaturated alcohol	Lactone (yield %)[a]	Saturated alcohol (yield %)
1	 **1**	 **18** (63)	 **1'** (-)[b]
2	 **2**	 **19** (45)	 **2'** (15)[a]
3	 **3**	 **20** (56)	 **3'** (-)[b]
4	 **4**	 **21** (65)	 **4'** (-)[b]
5	 **6**	 **22** (70)	 **6'** (10)[a]

[a] Isolated yields. [b] Not detected by GC/MS.

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(3) Schoevaart, R.; van Rantwijk F.; Sheldon R. A. *J. Org. Chem.* **2000**, *65*, 6940−6943. (b) Zimmermann, F. T.; Schneider, A.; Schörken, U.; Sprenger, G. A.; Fessner, W.-D. *Tetrahedron: Asymmetry* **1999**, *10*, 1643−1646. (c) Gijsen, H. J. M.; Wong, C.-H. *J. Am. Chem. Soc.* **1995**, *117*, 2947−2948

(4) Son, S. U.; Park, K. H.; Chung, Y. K. *J. Am. Chem. Soc.* **2002**, *124*, 6838−6839. (b) Drouin, S. D.; Zamanian, F.; Fogg, D. E. *Organometallics* **2001**, *26*, 5495−5497. (c) Evans, A.; Robinson, J. E. *J. Am. Chem. Soc.* **2001**, *123*, 4609−4610. (d) Jeong, N.; Seo, S. D.; Shin, J. Y. *J. Am. Chem. Soc.* **2000**, *122*, 10220−10221. (e) Barnhart, R. W.; Bazan, G. C.; Mourey T. *J. Am. Chem. Soc.* **1998**, *120*, 1082−1083. (f) Takayoshi, A.; Sasai, H.; Aoe, K.-I.; Okamura, K.; Date, T.; Shibazaki, M. A*ngew. Chem., Int. Ed. Engl.* **1996**, *35*, 104−106.

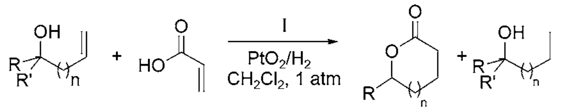
(5) Purchased from Aldrich.

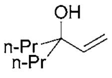
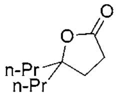
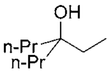
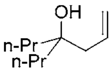
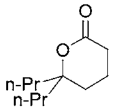
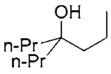
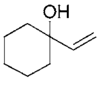
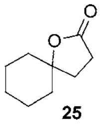
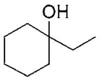
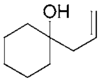
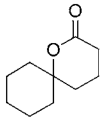
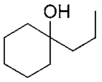
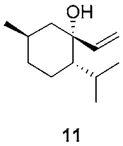
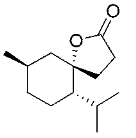
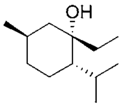
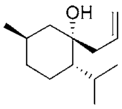
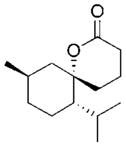
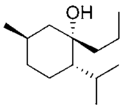
(6) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168−8179.

(7) Cossy, J.; Bargiggia, F.; BouzBouz, S. *Tetrahedron Lett.* **2002**, *43*, 6715−6717.

(8) For example, see: (a) Paddon-Jones, G. C.; Moore, C. J.; Brecknell, D. J.; König, W. A.; Kitching, W. *Tetrahedron Lett.* **1997**, *38*, 3479−3482. (b) Kula, J.; Sikora, M.; Sadowska, H.; Piwowarski, J. *Tetrahedron* **1996**, *52*, 11321−11324. (c) Bloch, R.; Gilbert, L. *J. Org. Chem.* **1987**, *52*, 4603−4605. (d) Ortuño, R. M.; Merce, R.; Font, J. *Tetrahedron* **1987**, *43*, 4497−4506. (e) Bravo, P.; Resnatl, G.; Vlanl, F.; Arnone, A. *Tetrahedron* **1987**, *43*, 4635−4647.

Table 3. Lactones from Tertiary Unsaturated Alcohols

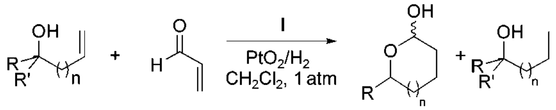


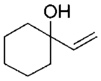
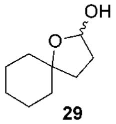
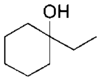
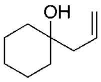
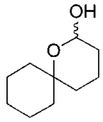
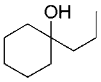
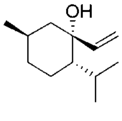
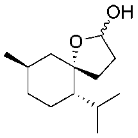
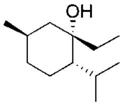
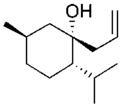
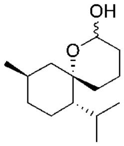
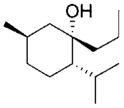
Entry	Unsaturated alcohol	Lactone (yield %)^{a}	Saturated alcohol (yield %)
1	 **7**	 **23** (53)	 **7'** (-)^{c}
2	 **8**	 **24** (42)	 **8'** (15)^{a}
3	 **9**	 **25** (57)	 **9'** (6)^{a}
4	 **10**	 **26** (50)	 **10'** (15)^{a}
5	 **11**	 **27** (-)^{b}	 **11'** (71)^{a}
6	 **12**	 **28** (35)	 **12'** (35)^{a}

^{a} Isolated yields. ^{b} Not detected by GC/MS. ^{c} Detected by GC/MS.

(0.05 equiv) under 1 atm of hydrogen[9] led to the formation of five-membered and six-membered ring lactones, respectively, in yields between 45 and 70%. The saturated alcohols were not detected by GC/MS. It is worth noting that in the case of allylic alcohol **5**, lactone **17** was isolated in 10% yield. This low yield is probably due to the fact that the benzyl ether functionality is sensitive to the hydrogenation conditions. The results are summarized in Table 1.

Table 4. Lactols from Tertiary Unsaturated Alcohols



Entry	Unsaturated alcohol	Lactone (yield %)^{a}	Saturated alcohol (yield %)
1	 **9**	 **29** (60)	 **9'** (-)^{c}
2	 **10**	 **30** (42)	 **10'** (-)^{b}
3	 **11**	 **31** (-)^{b}	 **11'** (42)^{a}
4	 **12**	 **32** (11)	 **12'** (70)^{a}

^{a} Isolated yields. ^{b} Not detected by GC/MS. ^{c} Detected by GC/MS.

It is worth noting that ruthenium catalyst **I** as well as PtO_2 do not catalyze the esterification of acids, ruling out an esterification/ring-closing metathesis/hydrogenation sequence (Scheme 2).

Substituted lactols are useful intermediates in synthesis as they are synthetic equivalents of ω-hydroxyaldehydes. By using a three-step one-pot reaction, five-membered and six-membered ring lactols were obtained from secondary allylic and homoallylic alcohols, respectively, when treated with acrolein (3 equiv) in the presence of ruthenium catalyst **I** (0.05 equiv) and PtO_2 (0.05 equiv) under 1 atm of hydrogen at room temperature. Under these conditions, lactols were isolated in good yields (45−70%). During this process small amounts of the saturated alcohols **2′** and **6′** were formed (yields <15%). The results are reported in Table 2.

Spirocyclic lactones and lactols can be synthesized in a three-step one-pot reaction from unsaturated tertiary alcohols from acrylic acid and acrolein, respectively. Spirocyclic

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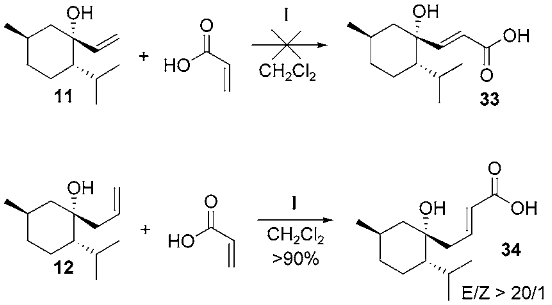
[9] Typical procedure for tandem cross-metathesis/hydrogenation reaction: In a 10 mL round-bottom flask, a solution of α,β-unsaturated carbonyl compound (3 equiv, 1.2 mmol) and allylic or homoallylic alcohol (1 equiv, 0.4 mmol) in CH_2Cl_2 (0.2 M, 2.5 mL) was degassed under vacuum and purged with H_2, and then catalyst **I** and PtO_2 were introduced. The reaction mixture was degassed again under vacuum and then vigorously stirred under 1 atm of hydrogen. After 15 h at room temperature, the solvent was evaporated and the residue was purified by flash chromatography to produce the corresponding lactol or lactone.

lactones were obtained in good yields (yield >40%) except when allylic alcohols **11** and **12** were used. In that case, lactone **27** was not detected (yield < 5%) and the saturated alcohol **11′** was isolated in 71% yield. Using the homoallylic alcohol **12** allowed lactone **28** to be isolated in 35% yield and the saturated alcohol **12′** in 35% yield. For these two latter alcohols **11** and **12**, the yield in lactones was not as high as that for alcohols **7**−**10** and the saturated alcohols **11′** and **12′** were formed in modest to high yields.

The same phenomena were observed in the three-step one-pot lactolization reaction, as spirocyclic lactols were obtained in high yields from tertiary alcohols **9** and **10** and in low yields from the tertiary alcohols **11** and **12** (Tables 3 and 4).

To verify if the cross-metathesis reaction could take place with the sterically hindered tertiary alcohols **11** and **12**, these two alcohols were treated with acrylic acid just in the presence of catalyst **I** at room temperature in CH_2Cl_2. Under these conditions the cross-metathesis product **33**, which could be obtained from **11**, was not detected (<5%). In contrast, the cross-metathesis compound **34** was obtained in good yield (>90%) and with high stereoselectivity (*E*/*Z* < 20/1) from alcohol **12** (Scheme 3). These results imply that when a sterically hindered allylic alcohol is treated with **I** and PtO_2 at room temperature, under 1 atm of hydrogen, the hydrogenation is faster than the cross-metathesis reaction.

Scheme 3



In conclusion, we have shown the usefulness of the combination of ruthenium catalyst **I** and PtO_2 in a three-step one-pot reaction for the construction of substituted lactones and lactols.

This tandem reaction is performed under very mild conditions (room temperature, 1 atm of hydrogen), and purification of the intermediate can be avoided. The sequence is general and useful for synthetic objectives, which will be reported in due course.

Supporting Information Available: Detailed experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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