ORGANIC LETTERS

2007
Vol. 9, No. 9
1821−1824

An Efficient Oxidative Lactonization of 1,4-Diols Catalyzed by Cp*Ru(PN) Complexes

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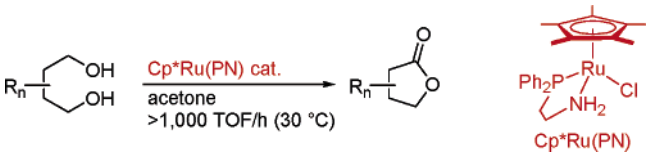
Received March 23, 2007

ABSTRACT



An efficient oxidative lactonization of 1,4-diols in acetone is accomplished by the well-defined ruthenium catalyst, whose bifunctional nature underlies the high efficiency as well as unique chemo- and regioselectivity of the reaction which provides a rapid access to γ-butyrolactones including flavor lactones hinokinin, and muricatacin.

Functionalized lactones are ubiquitous frameworks in a variety of biologically active natural products including antibiotics, lignans, pheromones, antifungal compounds, and flavor components.[1−3] Although a number of methods for the synthesis of lactones have been reported,[1] the oxidation of diols to lactones is a potentially useful process, and Fétizon oxidation using an excess amount of silver carbonate[1e,f] has long been a reliable method owing to its experimental convenience. Nonetheless, a more environmentally benign process that generates minimal heavy metal waste would be highly desirable. Although the metal-catalyzed oxidation of alcohols with nonhazardous oxidants may offer a practical solution,[4] its application to the oxidative lactonization of diols is still limited[2] mainly due to the intrinsic difficulty in the selective two-step oxidation of a primary alcoholic group over another alcoholic groups in the same molecules.[5]

We have recently developed Cp*Ru(II) catalyst systems bearing a series of chelating primary amine ligands with characteristic "NH/metal bifunctional units"[6] for highly effective organic transformations.[7] One of the most intriguing features of the catalyst system Cp*RuCl[$Ph_2P(CH_2)_2NH_2$-

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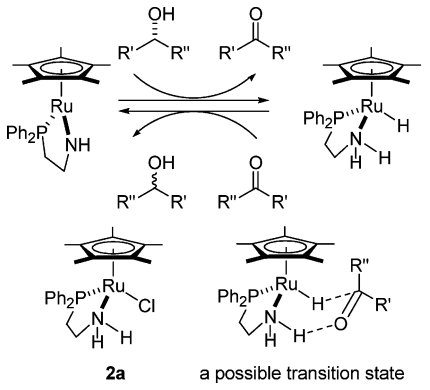
10.1021/ol0706408 CCC: $37.00
Published on Web 04/05/2007

κ^2-*P*,*N*] (**2a**) with KO-*t*-Bu is its extremely high activity for the cleavage of α-C−H bonds of *sec*-alcohols, which may result from *reversible* hydrogen transfer between alcohols and carbonyls, leading to a rapid racemization of chiral nonracemic *sec*-alcohols as illustrated in Scheme 1.[7c]

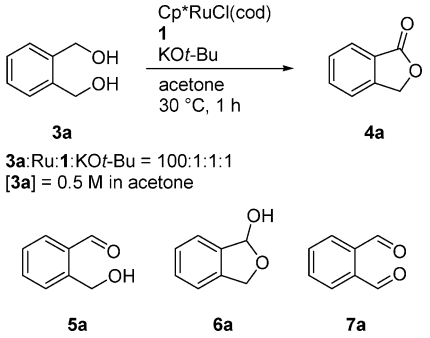
Scheme 1. Racemization Catalyzed by **2a** and Base System



In addition, we observed a significant rate enhancement in the catalytic intramolecular H−D scrambling of a *prim*-alcohol, benzyl-α,α-d_2-alclohol, compared with a *sec*-alcohol, 1-phenyl-1-d_1-ethanol.[8] These results led us to explore oxidative transformations with high preference for primary alcohols over secondary ones, and now we have found that a variety of 1,4-diols with a primary hydroxyl at one end are efficiently dehydrogenated to lactones in acetone, which contains the catalyst system of **2a** and KO-*t*-Bu under mild conditions. In this paper, we describe the scope of this oxidative lactonization using this bifunctional catalyst system.

Initial experiments focused on the acceleration effect of several ligands (**1**) on the reaction of 1,2-benzenedimethanol (**3a**) in acetone (Scheme 2).

Scheme 2. Ligand Effect in Oxidative Lactonization of **3a**



The reaction of **3a** was carried out in acetone containing Cp*RuCl(cod) (COD = 1,5-cyclooctadiene), a ligand, and KO-*t*-Bu (**3a**/Ru/**1**/KO-*t*-Bu = 100:1:1:1, [**3a**] = 0.5 M) at 30 °C for 1 h. The reaction hardly proceeded without any ligand to give phthalide (**4a**) in <1% yield. By contrast, addition of $Ph_2P(CH_2)_2NH_2$ (**1a**) brought about the very rapid reaction to produce **4a** in >99% yield under otherwise identical conditions.[9] While $Ph_2P(CH_2)_2NH(CH_3)$ (**1b**) worked equally well (>99% yield), neither $Ph_2P(CH_2)_2N(CH_3)_2$ (**1c**) nor $Ph_2P(CH_2)_2PPh_2$ (**1d**) promoted the reaction (5% and 0% yields, respectively). These results strongly suggest that the amino NH group plays a crucial role in the catalysis. Notably, the conventional Ru catalysts, $RuH_2(PPh_3)_4$[2b] and $Ru_3(CO)_{12}$,[2c] which have been known to effect the same reaction, turned out to be less efficient, giving **4a** in 17% and 0% yield respectively, under otherwise identical conditions. Oxidative lactone formation from the diols normally proceeds via lactol intermediates in equilibrium with one-step oxidized hydroxyaldehydes. However, no detectable amount of chemical species except **3a**, **4a**, acetone, and 2-propanol was observed by ^{1}H NMR spectroscopy throughout the reaction of **3a** using the present Cp*Ru-based catalyst system. Accordingly, we believe that the oxidation of **6a** into **4a** as well as the cyclization of **5a** into **6a** should be much faster than oxidation of **3a** into **5a** in the present reaction.[10] The possibility of a Tischenko-type mechanism involving the intermediacy of dialdehyde **7a** was ruled out by a separate experiment using **7a**, which resulted in the complete recovery of **7a** under similar conditions. Therefore, the unique metal/NH bifunctionality of the active catalyst shown in Scheme 1 should be responsible not only for the dehydrogenation from **3a** into **5a** but also from **6a** into **4a**, which stands in sharp contrast with the conventional catalysts $RuH_2(PPh_3)_4$[2b,f] or $Ru_3(CO)_{12}$[2c] that have been proposed to dehydrogenate alcohols via Ru alkoxide intermediates.

A variety of 1,4-diols **3b**−**q** (Figure 1) were rapidly convertible to the γ-butyrolactones **4b**−**q** in acetone (0.5 M) containing **2a** and KO-*t*-Bu as catalyst (1−3 mol %) at 30 °C within a few hours. The substituents in *cis*- (**3b**−**k**) and *trans*-2,3-disubstitued symmetrical diols (**3l**,**m**) hardly hinder the reaction to furnish the corresponding lactones including hinokinin (**4m**), one of the biologically important lignans. Of particular note is the excellent chemoselectivity in the reaction of diols bearing an olefinic group (**3i**−**k**) which remains intact despite possible saturation via intramolecular

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(8) For example, 1-phenyl-1-d_1-ethanol required 1 h to turn into equimolar mixtures of $PhCH(CH_3)OD$ and $PhCD(CH_3)OH$, whereas benzyl-α,α-d_2-alcohol took only 0.5 h to change into statistical mixtures of $PhCHDOH$ and $PhCD_2OH$ in a toluene solution containing **2a** and KO-*t*-Bu (0.2 mol %) at 30 °C.

(9) Separate experiments in varying substrate/acetone ratios under otherwise identical conditions indicated that the TOF of this reaction (TOF: turnover frequency, h^{-1}) increases with higher substrate concentration and it exceeds over 1000 TOF at 1.0 M.

(10) Katsuki's group reported that RuCl(NO)(salen) catalysts effect a unique aerobic lactol formation from diols under photoirradiation, in which the products are not further oxidized to lactones.[2n,o]

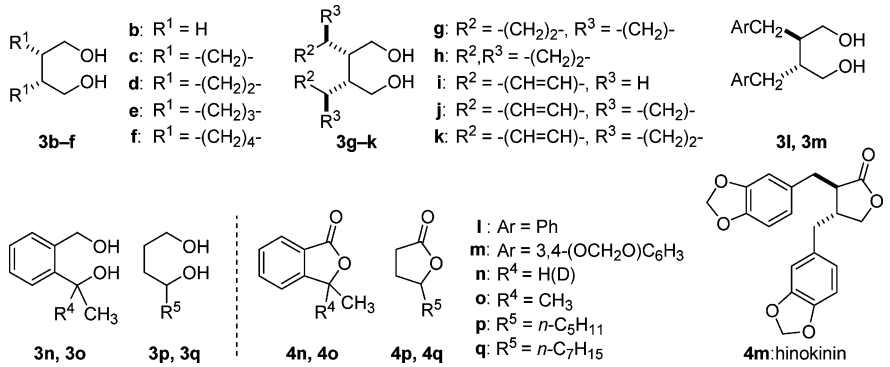
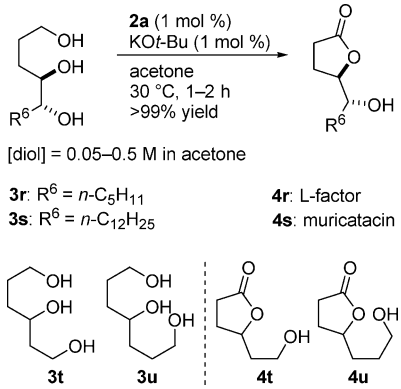


Figure 1. Applicable 1,4-diols (**3**) and their products (**4**).

hydrogen transfer. Unsymmetrical 1,4-diols **3n**−**q** with at least one primary OH group were also oxidized in acetone to give the lactones **4n**−**q** including flavor lactones **4p** and **4q** very efficiently. These results indicate that secondary or tertiary hydroxyl groups in **4n**−**q** only participate in the lactone formation as nonoxidized alcoholic counterparts. In fact, the deuterium atom in **3n**-d_1 (96% atom D) was completely preserved in the oxidation to give **4n**-d_1 (96% atom D). This result clearly indicates that dehydrogenation of the primary alcohol is much faster than that of the secondary group or the lactol formation.

In contrast to the very rapid oxidation of 1,4-diols, 1,5-diols need a larger amount of acetone and slightly longer reaction times. For example, the reaction of 1,5-pentanediol in acetone at a lower concentration (0.05 M, 1 mol %, 30 °C) gave δ-valerolactone in 81% yield only after 4 h. Moreover, 1,6-hexanediol afforded no ϵ-caprolactone under similar conditions, and a substantial amount of the starting material was recovered. This significant rate difference becomes synthetically attractive when triols[2i] are used as the substrates as shown in Scheme 3.

Scheme 3. Oxidative Lactonization of Triols



For example, the oxidative lactonization of triols **3r**−**u** resulted in the exclusive formation of γ-butyrolactones **4r**−**u** including L-factor (**4r**) and muricatacin (**4s**) where the remote OH groups remain intact regardless of whether they are primary or secondary. It should be noted that no measurable amount of other isomeric lactones were obtained in these reactions.

On the other hand, introduction of some tethers, suitable for cyclization, into a 1,5- or 1,6-diol caused facile lactone formation. The diol **3v** (Figure 2) with a rigid naphthalene

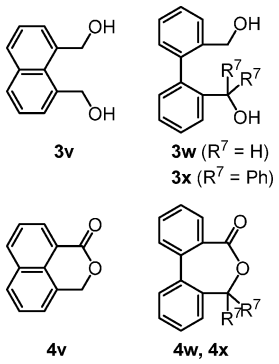


Figure 2. Applicable 1,5- and 1,6-diols and their products.

backbone was very rapidly convertible at 30 °C with 1 mol % of the catalyst into the corresponding δ-lactone **4v** (>99% yield after 1 h), and even diols **3w** or **3x** with biphenyl backbone afforded the corresponding ϵ-lactones **4w** and **4x** quantitatively (93% yield after 2 h and >99% yield after 3 h, respectively).

In summary, we have demonstrated that the catalyst system of **2a** and KO-*t*-Bu is a highly effective catalyst for the oxidative lactonization of a wide variety of diols in acetone, in which acetone can be used as a reaction solvent and a cheap hydrogen acceptor. Due to its high efficiency and experimental simplicity, the present catalytic method can provide a powerful and environmentally benign alternative for Fétizon oxidation. Further studies on its application to stereoselective lactone synthesis are in progress in our laboratory.

Acknowledgment. Support of this research was provided by the Ministry of Education, Culture, Sports, Science and Technology of Japan (Nos. 16750073 and 18065017) and by Taisho Pharmaceutical Co. Ltd. and the Asahi Glass Foundation (M.I.).

Supporting Information Available: Experimental procedures, characterization data, and deuterium-labeling experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0706408