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Lactonization of Diols Catalyzed by Cp*Ru Complexes Bearing Primary Amine Ligands

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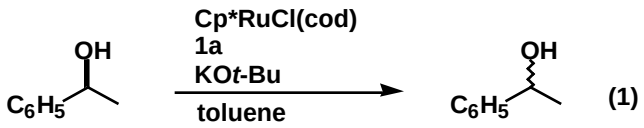
Abstract: The rapid lactonization of α,ω-diols is accomplished by Cp*Ru complexes (Cp* = pentamethylcyclopentadienyl, η^5-$C_5(CH_3)_5$) bearing P–N chelate ligands as a catalyst in acetone. Both tertiary phosphino and primary amino groups in the P–N ligand are crucially important for the catalytic activity.

Although catalytic transformation of primary alcohols to carboxylic acid derivatives is of importance in view of industrial process and synthetic means, there have been only a limited number of reports with modest catalytic activity.[1] During the course of our study on the design of Cp*Ru complexes bearing primary amine ligands and their catalysis,[2] we have found that a combined catalyst system of Cp*Ru(II) complex, P–N chelate ligand, and base is highly effective for racemization of optically active secondary alcohols. For example, optically active 2-phenylethanol (>99% ee) is completely racemized within 1 h at 30 °C in the presence of 1 mol % of Cp*Ru(cod), 2-diphenylphosphinoethylamine (**1a**), and KO*t*-Bu (COD = 1,5-cyclooctadiene) (eq.1).

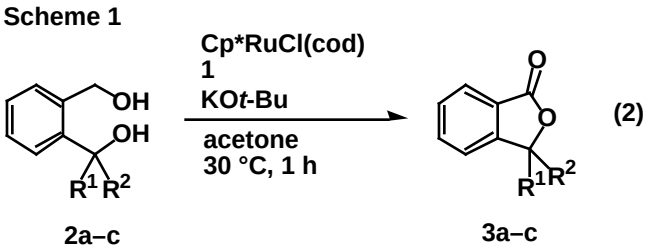


alcohol:Ru:1a:KO*t*-Bu = 100:1:1:1

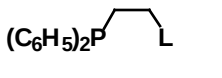
This racemization[3] can be explained by very rapid hydrogen transfer between secondary alcohols and the resulting carbonyl compounds caused by the catalyst system (476 TOF, TOF: turnover frequency, moles of product per mole of catalyst per hour, h^{-1}) These results prompted us to investigate dehydrogenative transformation of primary alcohols with this newly developed catalyst system and we have found that α,ω-diols undergo dehydrogenative lactonization in the presence of acetone very efficiently under mild condition.

The acceleration effect of several ligands in the lactonization of 1,2-benzenedimethanol (**2a**) was examined (eq.2).

Scheme 1



2:Ru:1:KO*t*-Bu = 100:1:1:1
2a: R^1, R^2 = H, 2b: R^1 = H (D), R^2 = CH_3, 2c: R^1, R^2 = CH_3

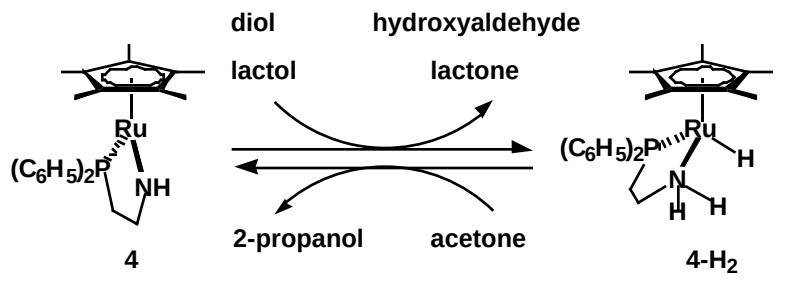


1a: L = NH_2 **1c: L = $N(CH_3)_2$**
1b: L = $NH(CH_3)$ **1d: L = $P(C_6H_5)_2$**

The reaction was carried out in acetone containing **2a** (0.5 M), Cp*RuCl(cod), ligand (**1**), and KO*t*-Bu (**2a**:Ru:**1**:KO*t*-Bu = 100:1:1:1) at 30 °C for 1 h. The reaction proceeded very slowly without any ligand, to give phthalide (**3a**) in <1% yield. However, the screening test with a range of P–N ligands listed in Scheme 1 under otherwise identical conditions revealed that 2-diphenylphosphinoethylamine (**1a**) exhibited the highest rate enhancement to afford **3a** quantitatively (>99% yield). The initial rate for the formation of **3a** catalyzed by Cp*RuCl(cod)–**1a**–KO*t*-Bu reached as high as 575 h^{-1}. 2-Diphenylphosphinoethyl-*N*-methylamine (**1b**) worked equally well (>99% yield), but 2-diphenylphosphinoethyl-*N*,*N*-dimethylamine (**1c**) hardly promote the reaction (5% yield). These results strongly suggest that the amino NH group plays a crucial role for the catalysis. This may be seen from the fact that 1,2-bis(diphenylphosphino)ethane (**1d**) was totally ineffective (0% yield). The previously reported catalysts, $RuH_2(P(C_6H_5)_3)_4$[1a] or $Ru_3(CO)_{12}$[1b], gave **3a** in 17% and 0% yield, respectively under otherwise identical conditions.

In the present reaction, diols are supposed to undergo dehydrogenation firstly to give hydroxyaldehydes and then the resulting hydroxyaldehydes are cyclized to lactols, which are further dehydrogenated to provide lactones. The latter dehydrogenation should be much faster than the first one, since no appreciable amount of hydroxyaldehyde or lactol was detected by ^{1}H NMR throughout the reaction. In addition, a considerable amount of 2-propanol was observed by ^{1}H NMR to form as a byproduct in the reaction mixture. A possibility for an intermediacy of dialdehyde was ruled out by the fact that phthalic dicarboxaldehyde remained unchanged when it is employed as a starting material under similar conditions. We believe that Cp*RuCl(cod)–**1a**–KO*t*-Bu catalyst system possibly serves *in situ* an active catalyst, Cp*Ru(amido) complex (**4**), which promotes the effective dehydrogenation of diol and lactol (Scheme 2).

Scheme 2



The significant role of NH functionality in **1** may suggest that the hydrogen transfer between **4** and **4-H_2** is facilitated by a six-membered transition state (Figure 1),[2] which leads to high efficiency superior to $RuH_2(P(C_6H_5)_3)_4$ or $Ru_3(CO)_{12}$.

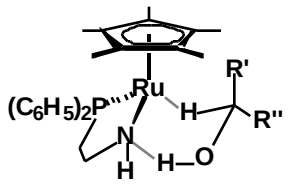
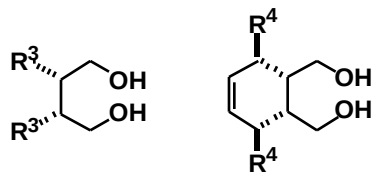


Figure 1. A possible six-membered transition state.

Phthalide derivatives **3b** or **3c** can be prepared within 1 h with Cp*RuCl(cod)–**1a**–KO*t*-Bu in acetone by oxidizing **2b** or **2c** in which at least one OH group is primary. Secondary or tertiary hydroxyl groups in **2b** or **2c** participate in the lactone formation as non-oxidized alcoholic counterparts. In fact, deuterium atom in **2b**-d_1 (96% atom D) was completely preserved in the oxidation to give **3b**-d_1 (96% atom D). This result clearly shows that dehydrogenation of primary alcohol is much faster than that of secondary group or lactol formation. Other 1,4-diols (**2d–j**) are also oxidized in acetone with Cp*RuCl(cod)-**1a**-KO*t*-Bu catalyst system to give γ-butyrolactones quantitatively (Figure 2). A variety of cycloalkane- (**2e–g**) and cycloalkene-1,2-dimethanols (**2h–j**) are quantitatively convertible within 1 h. Olefinic groups in **2h–j** remain intact in the reaction.



d: R^3, R^3 = H
e: R^3, R^3 = -(CH_2)-
f: R^3, R^3 = -$(CH_2)_2$-
g: R^3, R^3 = -$(CH_2)_4$-
h: R^4, R^4 = H
i: R^4, R^4 = -(CH_2)-
j: R^4, R^4 = -$(CH_2)_2$-

Figure 2. 1,4-butanediols leading to γ-butyrolactones.

In contrast to very rapid lactonization of 1,4-diols, 1,5-diols need slightly longer reaction time. For example, oxidation of 1,5-pentanediol to δ-valerolactone takes 5 h for completion. Moreover, 1,6-hexanediol afforded no ε-caprolactone under similar conditions and substantial amount of the starting material was recovered. However, introduction of some tethers suitable for cyclization, into 1,5- or 1,6-diol caused facile lactone formation (Figure 3).

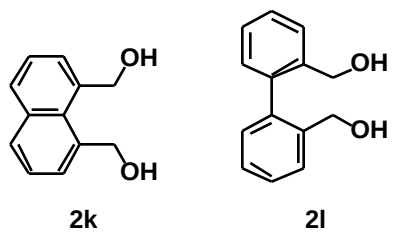


Figure 3. 1,5-, or 1,6-diols leading to lactones.

Thus, 1,5-diol **2k** was very rapidly converted into the corresponding δ-lactone (>99% conv after 1 h) and even 1,6-diol **2l** did afford the corresponding ε-lactone quantitatively (>99% conv after 2 h). The successful cyclization of **2l** may be attributable to the free rotation of its biaryl axis. In contrast, chiral 1,1'-binaphthalene-2,2'-dimethanol with conformationally locked biaryl axis remained unchanged after the reaction.

Regiochemistry for the present lactonization is delicately influenced by the structures of the diols (Figure 4). When *gem*-dimethyl groups are introduced at 2-position of 1,4-butanediol (**2m**), **3m** and **3m'** were obtained in >99% yield with the regioselectivity as high as 95:5. The selective formation of **3m** indicated that the present catalyst preferentially dehydrogenates

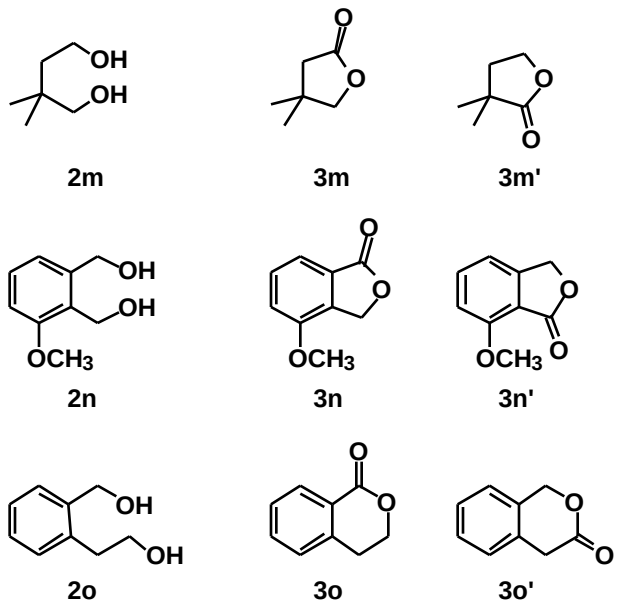


Figure 4. Unsymmetrical diols and their products.

sterically less hindered primary OH group. On the other hand, 3-methoxy-1,2-benzenedimethanol (**2n**) gave **3n** and **3n'** in >99% yield with a 26:74 molar ratio. In this case, a hydrogen bonding between OH group at 2-position and etheral oxygen at 3-position may be ascribable to the favorable dehydrogenation of 2-hydroxylmethyl group in spite of its steric congestion. Furthermore, it was shown that OH group at benzylic position is oxidized in preference to normal OH group by the regioselectivity of 74:26 for **3o** and **3o'**, observed in the lactonization of **2o**.

In summary, we have found that Cp*RuCl(cod)–**1a**–KO*t*-Bu ternary catalyst system is a highly effective catalyst for lactonization of a variety of α,ω-diols in acetone. Although lactonization of diols have long been relying onto the Fétizon reagent, in which a stoichiometric amount of silver waste are produced,[4] our protocol can be a powerful and environmentally benign alternative. Further studies on catalytic asymmetric lactonization by using chiral catalysts are in progress in our laboratory.

References.

1 (a) S.-I. Murahashi, K. Ito, T. Naota, and Y. Maeda, *Tetrahedron Lett.* **22**, 5327 (1981). (b) Y. Shvo, Y. Blum, D. Reshef, and M. Menzin, *J. Organomet. Chem.* **226**, C21 (1982). (c) Y. Ishii, K. Osakada, T. Ikariya, M. Saburi, and S. Yoshikawa, *J. Org. Chem.*, **51**, 2034 (1986) and references therein.

2 M. Ito, M. Hirakawa, K. Murata, and T. Ikariya, *Organometallics* **20**, 379 (2001).

3 (a) J. H. Koh, H. M. Jeong, and J. Park, *Tetrahedron Lett.*, **39**, 5545 (1998). (b) B. A. Persson, A. L. E. Larsson, M. L. Ray, and J. E. Bäckvall, *J. Am. Chem. Soc*. **121**, 1645 (1999) and references therein. (c) C. P. Casey, S. W. Singer, D. R. Powell, R. K. Hayashi, and M. Kavana, *ibid* **123**, 1090 (2001).

4 For example, D. K. M. Duc, M. Fétizon, and M. Kone, *Bull. Soc. Chim. Fr*. 2351 (1975).