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Ruthenium-Promoted Acceptorless and Oxidant-Free Lactone Synthesis in Aqueous Medium

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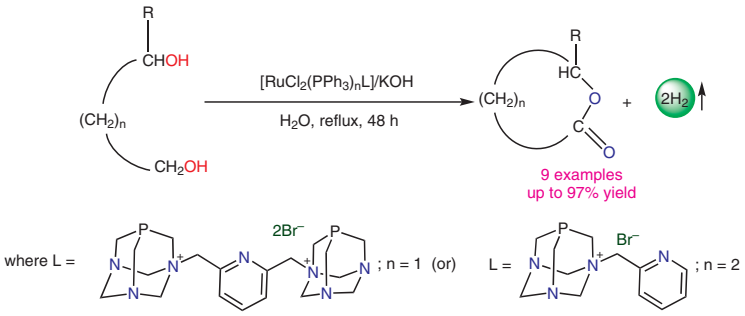

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Abstract Ruthenium-catalyzed formation of lactones from diols in aqueous medium has been demonstrated. 1,3,5-Triazaphosphaadamantane (PTA) included water-soluble ruthenium complexes [$RuCl_2(PPh_3)(2,6\text{-Py-}(CH_2\text{-PTA})_2]\cdot 2Br$ and $[RuCl_2(PPh_3)_2(2\text{-PyCH}_2\text{PTA})]\cdot Br$ in the presence of KOH were found to be efficient for the synthesis of lactones from diols. The reported synthetic protocol is green as it uses water as solvent, avoids the use of any hydrogen acceptor/oxidant, and produces hydrogen as the only side product. Mechanistic studies revealed that lactone formation involved aldehyde intermediate and followed dehydrogenative pathway.

Key words diol, aqueous catalysis, dehydrogenation, lactone

Lactones or cyclic esters are one of the most important classes of compounds which are widely present structural motifs in natural and synthetic compounds. Lactones are also being used as intermediates and solvents in several reactions.[1] As a result, a plethora of methods are available for the synthesis of lactones. The traditional methods reported in literature for the synthesis of lactones involved oxidative esterification of diols in the presence of various oxidants in stoichiometric amount which suffer from poor atom economy.[2] Another synthetic strategy which employs transition-metal catalysts for the dehydrogenative lactonization of diols with the elimination of hydrogen was found to be very attractive for the synthesis of lactones. Dehydrogenative lactonization of diols was often carried out in the presence of sacrificial amount of hydrogen acceptors. For example, Lin et al. reported the conversion of diols into lactones in the presence of iridium polyhydride catalyst in tandem with acetone as hydrogen acceptor.[3a] Hiroi and co-workers reported the oxidative conversion of a variety of 1,4- and 1,5-diols into lactones with a Cp*Ir catalyst bearing an amino alcohol ligand using acetone or butanone as hydrogen acceptor.[3b] Ikaria et al. reported the ruthenium-catalyzed conversion of diols into lactones using acetone as hydrogen acceptor.[3d] The use of sacrificial hydrogen acceptors makes this synthetic protocol less atom economic and inferior from the green chemistry point of view. Observing dehydrogenative lactonization under acceptorless conditions with the evolution of hydrogen is quite challenging. Murahashi and his co-workers have reported the metal-catalyzed acceptorless dehydrogenation of diols to lactones which is accompanied by the elimination of hydrogen gas.[3c] Yamaguchi et al. reported the acceptorless lactonization of diols using Ir catalyst.[3e] The advent of green organometallic chemistry in combination with outstanding catalytic activities of transition-metal complexes towards acceptorless alcohol dehydrogenation (AAD) have increased the demand for water soluble metal complexes.[4,5] Although various catalysts have been reported for the acceptorless dehydrogenation of diols to lactones in organic medium, reports on catalytic systems that work in aqueous medium are scarce.[6] To the best of our knowledge there is only one report available on the Cp*Ir system catalyzed lactone synthesis in aqueous medium reported by Yamaguchi and his co-workers (Figure 1).[3e]

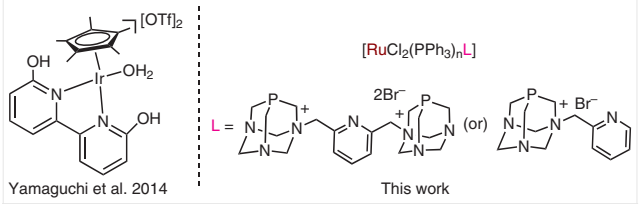
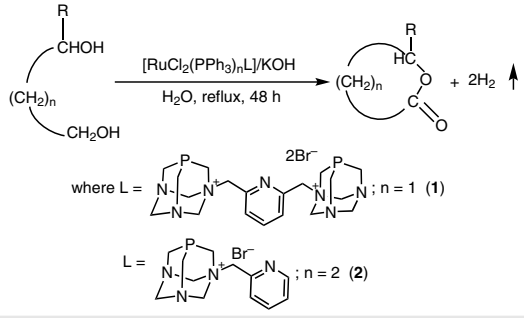


Figure 1 Transition-metal complexes used for dehydrogenative lactonization in aqueous medium

Several phosphine ligands that are known to induce water solubility to the transition-metal complexes are ionic in nature.[7] In addition to ionic phosphine ligands, few nonionic water-soluble cagelike phosphines are also known in the literature for this purpose. A few examples of cagelike phosphine ligands comprises Vercade-type phosphines, adamantane-like 1,3,5-triaza-7-phosphaadamantane (PTA), etc.[7] Our group is mainly focusing on exploring the reactivity of PTA ligands because of several advantages of PTA over other phosphine ligands. In addition, PTA-coordinated transition-metal complexes are well-known in the field of aqueous catalysis.[8] Notable examples of catalytic reactions promoted by Ru–PTA complexes are isomerization of linear allylic alcohols by Romeroso and co-workers,[9] hydration of nitriles to form amides reported independently by Gimeno, Frost, and their co-workers,[10] aqueous-phase hydrogenation of carbon dioxide and bicarbonate by Laurenczy et al.[11a] The hydrogen-borrowing methodology was used by Peruzzini and co-workers for the synthesis of amines.[11b] Recently, our group reported the ruthenium-mediated conversion of alcohols into the corresponding carbonyl compounds using PTA- and pyridine-included chelating-ligands-coordinated $[RuCl_2(PPh_3)(2,6\text{-Py-}(CH_2\text{-PTA})_2]\cdot 2Br$ (**1**) and $[RuCl_2(PPh_3)_2(2\text{- PyCH}_2\text{PTA})]\cdot Br$ (**2**) complexes in aqueous medium.[12]

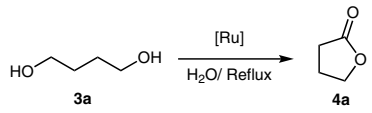
Herein, we reported the acceptorless dehydrogenative lactonization of diols to form lactones using PTA- and pyridine-containing chelating-ligands-coordinated complexes $[RuCl_2(PPh_3)(2,6\text{-Py-}(CH_2\text{-PTA})_2]\cdot 2Br$ (**1**) and $[RuCl_2(PPh_3)_2(2\text{-PyCH}_2\text{PTA})]\cdot Br$ (**2**) in aqueous medium (Scheme 1). We have also experimentally proved the formation of ruthenium hydride as active catalyst and aldehyde intermediate during the synthesis of lactones from diols.



Scheme 1 Acceptorless dehydrogenation of diols in aqueous medium

Recently, our group explored the catalytic activities of complexes **1** and **2** for the acceptorless alcohol dehydrogenation (AAD) in aqueous medium,[12] which prompted us to test both the complexes for the oxidation of diols.Catalytic dehydrogenation of 1,4-butanediol (**3a**) in water was taken as the model reaction for the optimization of reaction conditions as shown in Table 1. Initially, we used the optimized conditions used for the oxidation of alcohol using both catalysts **1** and **2**.[12] Thus, using 5 mol% of ruthenium complex and 15 mol% KOH as base, under water reflux conditions for 48 h, resulted in moderate yield of butyrolactone (**4a**, Table 1, entries 1 and 2). Increase in catalyst/base loadings to 7.5/22.5 mol% led to slight improvement in the yield of lactone product (Table 1, entries 3 and 4). When catalyst loading was increased further to 10 mol%, very good yield of product **4a** was obtained while using both complexes **1** and **2** (Table 1, entries 5 and 6). In view of reducing the base amount, reactions were attempted with 25 mol% of KOH and resulted in very good yield of lactone (Table 1, entries 9 and 10). Further decrease in base loading resulted in decrease in yield of lactone (Table 1, entries 11 and 12). In order to compare the role of PTA with PPh_3, we tested $RuCl_2(PPh_3)_3$ as catalyst for lactonization of diols under similar reaction conditions, which resulted in trace amount of lactone (Table 1, entry 13). Li and his co-workers have reported the use of $RuCl_2(PPh_3)_3$ as catalyst for the isomerization of allylic alcohols in water.[13]

Table 1 Optimization of Reaction Conditions for Catalytic Lactonization of 1,4-Butanediol (**3a**)[a]



3a **4a**

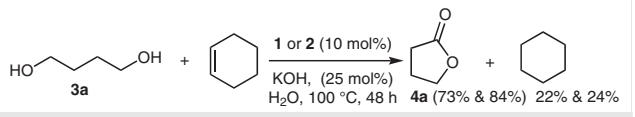
Entry	Catalyst (mol%)	KOH (mol%)	Time (h)	Yield of **4a** (%)[b]
1	**1** (5)	15	48	45
2	**2** (5)	15	48	57
3	**1** (7.5)	22.5	48	67
4	**2** (7.5)	22.5	48	75
5	**1** (10)	30	48	84
6	**2** (10)	30	48	95
7	**1** (10)	30	36	78
8	**2** (10)	30	36	86
9	**1** (10)	25	48	80
10	**2** (10)	25	48	93
11	**1** (10)	20	48	62
12	**2** (10)	20	48	78
13	$RuCl_2(PPh_3)_3$	25	48	traces

[a] *Reaction conditions*: Reactions were carried out with **3a** (0.5 mmol), [Ru], and KOH in H_2O (0.6 mL) under reflux.
[b] GC yield using dodecane as internal standard and average of at least two runs.

Having the optimized conditions in hand, we explored the catalytic activities of both complexes **1** and **2** for the dehydrogenative lactonization of various diols as summarized in Table 2.[14] While using both **1** and **2**, a variety of diols have been dehydrogenated in aqueous media to form lactones with four-, five-, and six-membered ring structures. It

was observed that complex **2** showed better catalytic activity as compared to complex **1**. As a beginning, few aliphatic diols were tested to afford four-, five-, and six-membered lactones in moderate to good yields (Table 2, entries 1–3). The primary hydroxy group of the asymmetrical diol **3d** having less hindered substituents was regioselectively oxidized to give β-substituted γ-butyrolactones (**4d**, Table 2, entry 4). This indicates that preferably the primary hydroxyl group was dehydrogenated in comparison to the secondary hydroxyl group. Lactonization of branched diols proceeded well with the formation of γ-butyrolactone (Table 2, entry 5). Benzylic diols were oxidized to give lactones in good yields (Table 2, entry 6 and 7). Allylic alcohol **3h** underwent dehydrogenative lactonization along with hydrogenation of the carbon–carbon double bonds to afford the product **4h** in good yield (Table 2, entry 8). The substituted cyclohexanol **3i** was also lactonized to form **4i** in good yield (Table 2, entry 9).

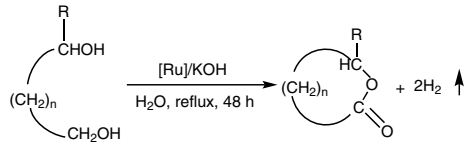
To investigate the mechanism for the dehydrogenative lactonization and hydrogen evolution, we carried out closed-vessel reactions of **1** and **2** catalyzed lactonization of 1,4-butanediol (**3a**) in the presence of cyclohexene as hydrogen acceptor (Scheme 2). When an aqueous solution containing 0.5 mmol of 1,4-butanediol, 5 mmol (10 equiv) of cyclohexene, and 10 mol% of **1** or **2** was heated to 100 °C for 48 h in a closed vessel, butyrolactone (**4a**) was observed with the formation of cyclohexane, as determined by gas chromatographic technique. The formation of cyclohexane in good yields confirmed the evolution of hydrogen during **1** or **2** catalyzed lactonization of diol.[15]

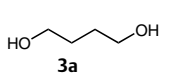
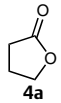
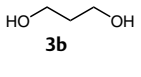
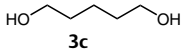
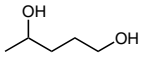
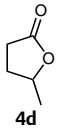
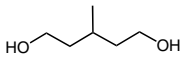
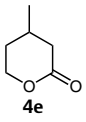
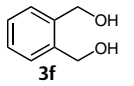
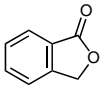
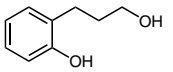
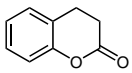
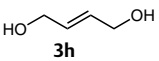
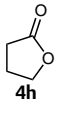
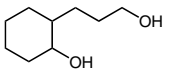
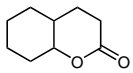


Scheme 2 Dehydrogenative lactonization of **3a** in the presence of cyclohexene using **1** and **2**

In view of getting further insight into the mechanism of dehydrogenative lactonization of diols using **1** and **2**, reactions were carried out in NMR tube, and ^{1}H NMR data were collected at different time intervals. In a typical NMR-tube reaction, a mixture of catalyst **1** or **2**, KOH, and 1,4-butanediol in D_2O was taken, heated at 100 °C before collecting the NMR data at different time intervals. When the mixture containing catalyst **1** was heated for 30 min, the NMR spectra showed two peaks around δ = –12.0 ppm which corresponds to Ru–H and a singlet at δ = 9.1 ppm attributed to aldehyde. Similar ^{1}H NMR pattern were obtained while using compound **2** as catalyst, which showed two peaks around δ = –12.4 ppm and a singlet at δ = 9.1 ppm, respectively, for the Ru–H and aldehyde groups. As the reactions progressed further, the peaks corresponding to Ru–H and aldehyde went on diminishing while using both the catalysts. The peaks corresponding to both hydride and aldehyde disappeared on heating the reaction mixtures for 5 h. These results indicated the formation of Ru–H and aldehyde as intermediate during the cyclization of diols. Based on the previous reports and our experimental observations, we have proposed the mechanism for conversion of diols into lactones in Scheme 3. Recently our group proved the mech-

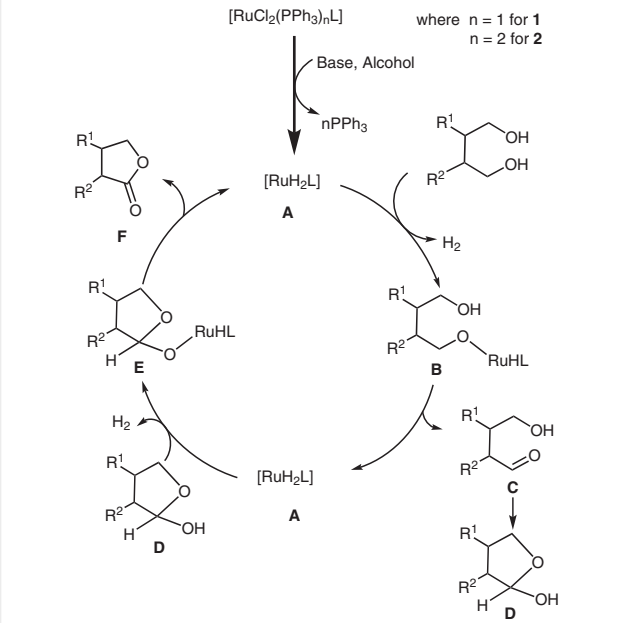
Table 2 Complex **1** and **2** Catalyzed Lactonization of Diols[a]



Entry	Substrate	Product	Isolated yield with **1** (%)	Isolated yield with **2** (%)
1	 **3a**	 **4a**	78	83
2	 **3b**	 **4b**	84	95
3	 **3c**	 **4c**	88	97
4	 **3d**	 **4d**	85	96
5	 **3e**	 **4e**	86	96
6	 **3f**	 **4f**	84	93
7	 **3g**	 **4g**	85	94
8	 **3h**	 **4h**	82	90
9	 **3i**	 **4i**	82	91

[a] *Reaction conditions*: Reactions were carried out with diol (4 mmol), **1** or **2** (10 mol%), and KOH (25 mol%) in H_2O (1.0 mL) under reflux for 48 h.

anism for AAD of alcohols using compounds **1** and **2** involved phosphine-dissociative pathway and ruthenium–hydride complex as active catalyst. The mechanism of dehydrogenative lactonization of alcohols is closely related to alcohol oxidation using **1**, **2**, and other reported catalysts.[16] According to this mechanism, both compounds **1** and **2** undergo triphenylphosphine dissociation followed by reaction with alcohol and base to generate the Ru–hydride active catalyst **A**. The active catalyst **A** undergoes oxidative addition with diol to form ruthenium alkoxide intermediate **B**, followed by elimination of hydrogen molecule. β-Hydrogen elimination of intermediate **B** resulted in hydroxyaldehyde **C**, which further undergoes cyclization to form lactol **D** to generate the active catalyst **A**. The active catalyst **A** undergoes oxidative addition with lactol **D**, followed by elimination of hydrogen molecule to yield the Ru–H intermediate **E**. Intermediate **E** further undergoes β-hydrogen elimination to form lactone **F** and the active catalyst **A**.



Scheme 3 Mechanism for the lactonization of diols with catalyst **1** and **2**

In conclusion, we have reported conversion of diols into lactones in aqueous medium using ruthenium complexes **1** and **2** bearing PTA and pyridine-based chelating ligands**.** We have also experimentally proved the formation of ruthenium hydride species as active catalyst and aldehyde intermediate.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1612247.

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(14) **General Procedure for Lactonization of Diols**
A Schlenk tube was charged with Ru complex **1** or **2** (10 mol%, 0.506 g or 0.512 g, 0.5 mmol), base (25 mol%, 0.070 g, 1.25 mmol), diol (5 mmol), and H_2O (1.0 mL). The resultant mixture was stirred under reflux for 48 h. On completion of the reaction, the product was extracted with DCM. All the solvent was evaporated under vacuo, and the product lactone was isolated from the crude mixture by silica gel column chromatography using hexane–EtOAc solvent mixture as eluent. The formation and purity of all the products were confirmed by comparing their ^{1}H NMR spectra with the reported values.

(15) **General Procedure for Lactonization of Diols in Presence of Hydrogen Acceptor**
An aqueous solution containing 1,4-butanediol (0.5 mmol), cyclohexene (5 mmol, 0.506 mL, 10 equiv), KOH (25 mol%, 0.007 g, 0.125 mmol), and **1** or **2** (10 mol%, 0.0506 g or 0.051 g, 0.05 mmol) was heated to 100 °C for 48 h in a sealed vessel. On completion of the reaction, the products were extracted with DCM and injected into gas chromatography. γ-Butyrolactone with 73% and 84% yields was observed with the formation of cyclohexane with 22% and 24% yields.

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