DOI: 10.1002/cctc.201300717

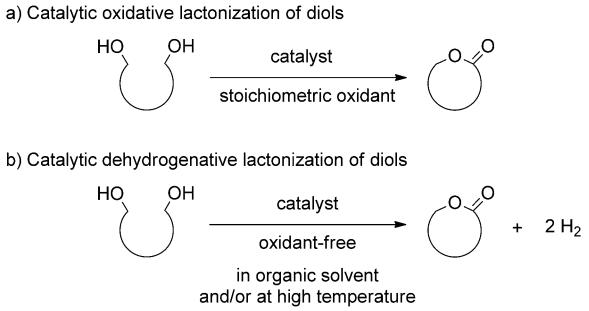
Dehydrogenative Lactonization of Diols in Aqueous Media Catalyzed by a Water-Soluble Iridium Complex Bearing a Functional Bipyridine Ligand

Ken-ichi Fujita,* Wataru Ito, and Ryohei Yamaguchi*[a]

A new catalytic system for the dehydrogenative lactonization of a variety of benzylic and aliphatic diols in aqueous media was developed. By using a water-soluble, dicationic iridium catalyst bearing 6,6′-dihydroxy-2,2′-bipyridine as a functional ligand, highly atom economical and environmentally benign synthesis of various lactones was achieved in good to excellent yields. Recovery and reuse of the catalyst were also accomplished by a simple phase separation and the recovered catalyst maintained its high activity at least until the fifth run.

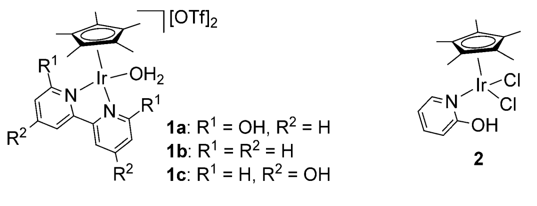
Introduction

Lactones are an important class of compounds in organic, bioorganic, and natural product chemistry. There are many methods for the synthesis of lactones that include the intramolecular esterification of hydroxy acids,[1] intramolecular hydroacyloxylation of olefinic acids,[2] and Baeyer–Villiger reaction of cyclic ketones.[3] The oxidative lactonization of diols (Scheme 1 a) is another important method for the production of lactones, and a number of catalytic systems have been studied that use environmentally acceptable oxidants such as oxygen,[4] hydrogen peroxide,[5] or acetone.[6] Very recently, catalytic systems that enable the oxidant-free lactonization of diols (Scheme 1 b) have attracted much attention and have been extensively studied.[7,8] In these catalytic systems, the lactonization proceeds without any oxidant with the accompanying evolution of H_2, which minimizes the environmental hazard and maximizes the atom efficiency. However, these reactions have to be performed in an organic solvent under reflux (>110 °C) or solvent-free conditions at a very high temperature (>200 °C).



Scheme 1. Previously reported catalytic lactonization of diols.

Meanwhile, we have continuously investigated the dehydrogenative reactions of alcohols[9] and cyclic amines[10] by using Ir catalysts bearing a functional ligand. In the course of our studies, we have developed a water-soluble Cp*Ir catalyst **1 a** (Cp*: pentamethylcyclopentadienyl) bearing 6,6′-dihydroxy-2,2′-bipyridine as a functional ligand, which exhibits a high catalytic performance for the dehydrogenation of primary and secondary alcohols to give carbonyl products in aqueous media.[9c] Inspired by these findings, we started to develop a new environmentally benign catalytic system for the dehydrogenative lactonization of diols that can be performed under reflux in water. The structures of the Cp*Ir catalysts used in this study are illustrated in Scheme 2.[11]



Scheme 2. Cp*Ir catalysts bearing a functional ligand used in the lactonization of diols in aqueous media.

Results and Discussion

Firstly, reactions of 1,2-benzenedimethanol (**3 a**) under various conditions were conducted to find the optimum conditions (Table 1). The dehydrogenative lactonization of **3 a** did not occur in the absence of catalyst (entry 1). Water-insoluble $[Cp^*IrCl_2]_2$ and water-soluble $[Cp^*Ir(H_2O)_3][OTf]_2$ bearing no functional ligand showed no catalytic activity (entries 2 and 3). If the solution of **3 a** in water was heated to reflux for 6 h in the presence of catalyst **1 a** (1.0 mol %), phthalide **4 a** was obtained in 98 % yield with high selectivity (entry 4). The evolution of H_2 was confirmed by analysis of the gas phase by using a hydrogen sensor. Additionally, the volume of H_2 was measured with a gas burette to give a 95 % yield of H_2 (footnote [c]

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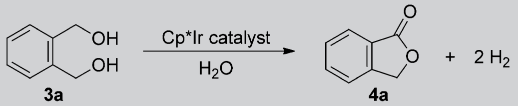
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/cctc.201300717.

in entry 4). Analogous catalysts **1b** and **1c** showed a lower activity than **1a**, which indicates that the α-hydroxy group in the functional ligand is indispensable for high catalytic performance (entries 5 and 6). Our previous catalyst **2**,[9a] which has a monodentate functional ligand, showed no activity (entry 7). Reactions with smaller amount of catalyst **1a** (entry 8), at a lower temperature (entry 9), and for a shorter reaction time (entry 10) resulted in lower yields of **4a** compared to that under the optimum conditions (entry 4).

To obtain reliable experimental evidence that the evolved gas in the lactonization of **3a** is H_2, we performed the following dual reactions (Scheme 3). The reaction of **3a** with catalyst **1a** was conducted in a flask that was connected by a rubber tube to another flask in which 1-decene and a catalytic amount of $RhCl(PPh_3)_3$ in benzene were placed. When the dehydrogenative lactonization of **3a** was almost completed, decane was produced in 82% yield in the latter flask, which demonstrates that the H_2 generated in the first flask was pure enough to reduce the 1-decene in the second flask.

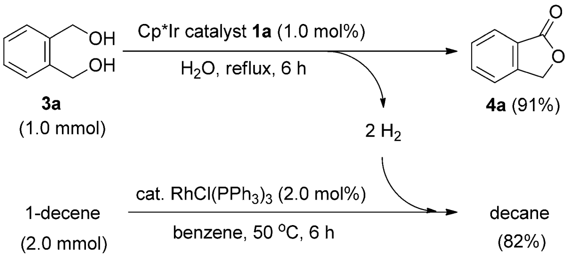
To evaluate the scope of this catalytic system, the reactions of various diols were conducted (Table 2). If the reactions of 1,2-benzenedimethanol derivatives **3b**–**3e** bearing an *ortho*, *para*-directing substituent at the 4-position were performed under reflux in water for 6 h in the presence of **1a** (1.0 mol%), isomeric mixtures of phthalide derivatives **4ba**–**4ea** and **4bb**–**4eb** were obtained in good to high yields. In these cases, the isomers with a substituent at the 5-position (**4ba**–**4ea**) were formed as major products (entries 2–5).[12] However, the reaction of **3f** that has a nitro group required a longer reaction time to give the product in a moderate yield with the selectivity opposite to that above (entry 6).[12] Reactions of **3g** and **3h** bearing a substituent at the 3-position gave phthalides **4ga** and **4ha**, respectively, predominantly in high yields (entries 7 and 8). The reactions of other benzylic diols **3i**–**3l** also gave five-, six-, and seven-membered lactones **4i**–**4l** in good to excellent yields (entries 9–12). The dehydrogenative lactonization of unsymmetrical diol **3m** proceeded well to give isomers

Table 1. Dehydrogenative lactonization of **3a** in aqueous media under various conditions.[a]

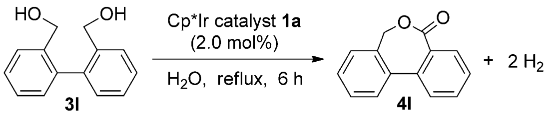


Entry	Catalyst [mol%]	T [°C]	t [h]	Conversion [%][b]	Yield [%][b]
1	–	reflux	6	0	0
2	$[Cp^*IrCl_2]_2$ (1.0)	reflux	6	0	0
3	$[Cp^*Ir(H_2O)_3][OTf]_2$ (1.0)	reflux	6	3	0
4[c]	**1a** (1.0)	reflux	6	100	98
5	**1b** (1.0)	reflux	6	47	3
6	**1c** (1.0)	reflux	6	45	41
7	**2** (1.0)	reflux	6	0	0
8	**1a** (0.2)	reflux	6	89	86
9	**1a** (1.0)	80 °C	6	10	10
10	**1a** (1.0)	reflux	1	41	41

[a] The reaction was performed with **3a** (1.0 mmol) and catalyst (1.0 or 0.2 mol%) in water (1.5 mL) under reflux. [b] Determined by ^1H NMR spectroscopy. [c] The yield of H_2 was 95% if the reaction was performed with **3a** (2.0 mmol) in water (3.0 mL).

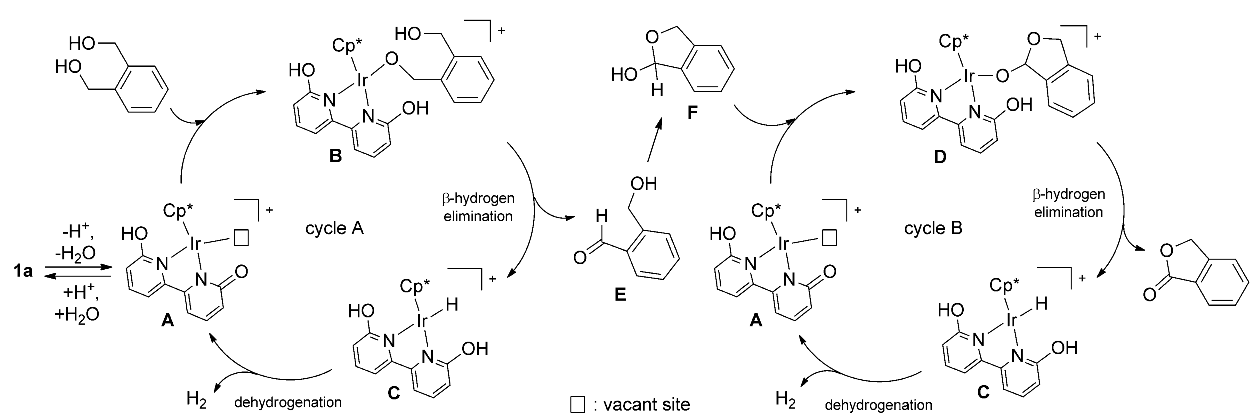


Scheme 3. Dual reactions that involve the dehydrogenative lactonization of **3a** and the hydrogenation of 1-decene.



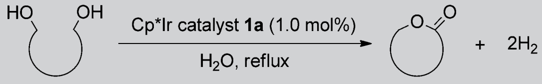
Cycle	1	2	3	4	5
NMR yield of **4l** [%]	99	99	95	93	93

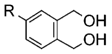
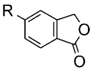
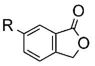
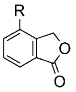
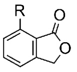
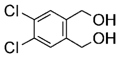
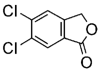
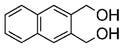
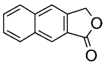
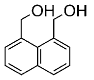
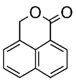
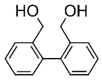
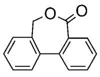
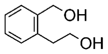
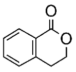
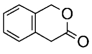
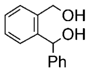
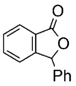
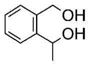
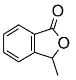
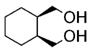
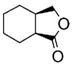
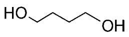
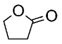
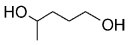
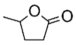
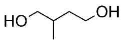
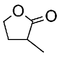
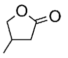
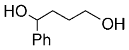
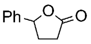
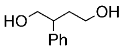
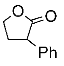
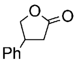
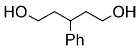
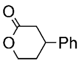
Scheme 4. Reuse of **1a**.



Scheme 5. A plausible mechanism for the dehydrogenative lactonization of **3a** catalyzed by **1a**.

Table 2. Dehydrogenative lactonization of various diols in aqueous media catalyzed by **1a**.[a]



Entry	Diol		*t* [h]	Product		Selectivity[b]	Yield [%][c]
							
1	R=H	**3a**	6	**4a**			97
2	R=Me	**3b**	6	**4ba**	**4bb**	55:45	92
3	R=OMe	**3c**	6	**4ca**	**4cb**	77:23	63[d]
4	R=Br	**3d**	6	**4da**	**4 db**	53:47	93
5	R=F	**3e**	6	**4ea**	**4eb**	67:33	94
6[e]	R=NO_2	**3f**	20	**4fa**	**4fb**	38:62	57
							
7	R=Me	**3g**	6	**4ga**	**4gb**	93:7	95
8	R=F	**3h**	20	**4ha**	**4hb**	81:19	89
9[f]		**3i**	20		**4i**		92
10[f]		**3j**	6		**4j**		78
11[f]		**3k**	6		**4k**		74
12		**3l**	6		**4l**		98
13		**3m**	20	 **4ma**	 **4mb**	86:14	88
14[g]		**3n**	6		**4n**		97
15[g]		**3o**	6		**4o**		91
16		**3p**	40		**4p**		68
17[g]		**3q**	20		**4q**		67[d]
18[e,h]		**3r**	20		**4r**		70
19		**3s**	20	 **4sa**	 **4sb**	60:40	64
20[e,h]		**3t**	20		**4t**		65
21		**3u**	20	 **4ua**	 **4ub**	45:55	93
22		**3v**	20		**4v**		52

[a] The reaction was performed with diol (1.0 mmol) and catalyst **1a** (1.0 mol%) in water (1.5 mL) under reflux. [b] The ratio of two isomers was determined by ^1H NMR spectroscopy of the crude products. [c] Isolated yield. [d] Determined by ^1H NMR spectroscopy. [e] 3.0 mol% of catalyst **1a** was used. [f] 3.0 mL of water was used. [g] 5.0 mol% of $NaHCO_3$ was added. [h] 15.0 mol% of $NaHCO_3$ was added.

4ma and **4mb** in a ratio of 86:14 (entry 13).[12] The addition of a catalytic amount of base ($NaHCO_3$) was effective to give lactones selectively in the reactions of diols that have a secondary alcoholic moiety (entries 14, 15, 18, and 20).[13] Not only aromatic diols, but also aliphatic ones could be used as substrates in the present catalytic system (entries 16–22), although the yields of lactones were relatively low in some cases.[14]

To demonstrate the advantages of the present catalytic system in aqueous media, the recovery and reuse of the catalyst were investigated (Scheme 4).[15] After the dehydrogenative lactonization of **3l** catalyzed by **1a** in water, the product **4l** could be isolated by simple extraction with an organic solvent. Catalyst **1a** could be recovered in the aqueous phase and reused for the next run. Notably, the recovered catalyst maintained its high activity at least until the fifth run.

A plausible mechanism for the present dehydrogenative lactonization of diols catalyzed by **1a** is shown in Scheme 5. The mechanism is closely related to that of the dehydrogenative oxidation of alcohols catalyzed by **1a**, which we have previously proposed.[9c] The initial step of the reaction would involve elimination of a proton (H^+) and aquo ligand from the dicationic catalyst **1a** to afford a monocationic unsaturated species **A** bearing an α-pyridonate-based functional ligand (cycle A). Then, the cooperative activation of one of the alcohol moieties in a diol could proceed to give an alkoxo species **B**. β-Hydrogen elimination in **B** would occur to afford a hydrido iridium species **C** and a hydroxyaldehyde intermediate **E**, which would be cyclized intramolecularly into a lactol **F**. The lactol **F** could be again activated and dehydrogenated by the active species **A** to give a lactone as the product (cycle B). Finally, the hydride in **C** would react with the hydroxyl proton on the functional ligand (ligand-promoted dehydrogenation) to release H_2 accompanied by the regeneration of the active species **A** (cycles A and B).

Conclusion

We have developed a new catalytic system for the dehydrogenative lactonization of diols in aqueous media. By using a water-soluble Cp*Ir catalyst **1a** (Cp*: pentamethylcyclopentadienyl), the highly atom-economical and environmentally benign synthesis of a variety of lactones was achieved. The recovery and reuse of the catalyst by a simple procedure were also accomplished. To the best of our knowledge, the present system is the first example of the dehydrogenative lactonization of diols in aqueous media.

Experimental Section

Dehydrogenative lactonization of diols in aqueous media catalyzed by 1 a

General procedure: Under an atmosphere of argon, **1 a** (1.0 or 3.0 mol %), water (1.5 or 3.0 mL), and diol (1.0 mmol) were placed in a flask. The mixture was stirred under reflux for 6–40 h. After the evaporation of the water under vacuum, the crude mixture was analyzed by ^{1}H NMR spectroscopy. Then, the product was isolated by column chromatography on silica gel (eluent: ethyl acetate/hexane).

Acknowledgements

This work was supported by KAKENHI (No. 19750075 and 25105732). We thank Masato Kobayashi, Ryuichi Tamura, and Shoichi Furukawa for their valuable technical assistance.

Keywords: alcohols · dehydrogenation · homogeneous catalysis · iridium · lactones

[1] a) J. March, *Advanced Organic Chemistry*, 3rd ed., Wiley, New York, **1985**, p. 348; b) T. Mukaiyama, *Angew. Chem.* **1979**, *91*, 798 – 812; *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 707 – 721.

[2] J. March, *Advanced Organic Chemistry*, 3rd ed., Wiley, New York, **1985**, p 686.

[3] a) J. March, *Advanced Organic Chemistry*, 3rd ed., Wiley, New York, **1985**, p. 990; b) H. Leisch, K. Morley, P. C. K. Lau, *Chem. Rev.* **2011**, *111*, 4165 – 4222.

[4] a) T. Nishimura, T. Onoue, K. Ohe, S. Uemura, *J. Org. Chem.* **1999**, *64*, 6750 – 6755; b) T. Mitsudome, A. Noujima, T. Mizugaki, K. Jitsukawa, K. Kaneda, *Green Chem.* **2009**, *11*, 793 – 797; c) Y. Endo, J.-E. Bäckvall, *Chem. Eur. J.* **2011**, *17*, 12596 – 12601.

[5] Q.-J. Zhu, W.-L. Dai, K.-N. Fan, *Green Chem.* **2010**, *12*, 205 – 208.

[6] a) S.-I. Murahashi, T. Naota, K. Ito, Y. Maeda, H. Taki, *J. Org. Chem.* **1987**, *52*, 4319 – 4327; b) T. Suzuki, K. Morita, M. Tsuchida, K. Hiroi, *Org. Lett.* **2002**, *4*, 2361 – 2363; c) M. Ito, A. Osaku, A. Shiibashi, T. Ikariya, *Org. Lett.* **2007**, *9*, 1821 – 1824.

[7] a) J. Zhao, J. F. Hartwig, *Organometallics* **2005**, *24*, 2441 – 2446; b) Y. Mikami, K. Ebata, T. Mitsudome, T. Mizugaki, K. Jitsukawa, K. Kaneda, *Heterocycles* **2010**, *80*, 855 – 861; c) S. Musa, I. Shaposhnikov, S. Cohen, D. Gelman, *Angew. Chem.* **2011**, *123*, 3595 – 3599; *Angew. Chem. Int. Ed.* **2011**, *50*, 3533 – 3537; d) J. Zhang, E. Balaraman, G. Leitus, D. Milstein, *Organometallics* **2011**, *30*, 5716 – 5724.

[8] The closely related dehydrogenative esterification of alcohols has been reported; a) J. Zhang, G. Leitus, Y. Ben-David, D. Milstein, *J. Am. Chem. Soc.* **2005**, *127*, 10840 – 10841; b) C. Gunanathan, L. J. W. Shimon, D. Milstein, *J. Am. Chem. Soc.* **2009**, *131*, 3146 – 3147; c) A. Sølvhøj, R. Madsen, *Organometallics* **2011**, *30*, 6044 – 6048; d) D. Spasyuk, S. Smith, D. G. Gusev, *Angew. Chem.* **2012**, *124*, 2826 – 2829; *Angew. Chem. Int. Ed.* **2012**, *51*, 2772 – 2775; e) M. Nielsen, H. Junge, A. Kammer, M. Beller, *Angew. Chem.* **2012**, *124*, 5809 – 5811; *Angew. Chem. Int. Ed.* **2012**, *51*, 5711 – 5713.

[9] a) K. Fujita, N. Tanino, R. Yamaguchi, *Org. Lett.* **2007**, *9*, 109 – 111; b) K. Fujita, T. Yoshida, Y. Imori, R. Yamaguchi, *Org. Lett.* **2011**, *13*, 2278 – 2281; c) R. Kawahara, K. Fujita, R. Yamaguchi, *J. Am. Chem. Soc.* **2012**, *134*, 3643 – 3646; d) R. Kawahara, K. Fujita, R. Yamaguchi, *Angew. Chem.* **2012**, *124*, 12962 – 12966; *Angew. Chem. Int. Ed.* **2012**, *51*, 12790 – 12794.

[10] R. Yamaguchi, C. Ikeda, Y. Takahashi, K. Fujita, *J. Am. Chem. Soc.* **2009**, *131*, 8410 – 8412.

[11] Cp* iridium complexes bearing similar functional ligands have been also reported by other research groups; a) W.-H. Wang, J. T. Muckerman, E. Fujita, Y. Himeda, *ACS Catal.* **2013**, *3*, 856 – 860; b) J. F. Hull, Y. Himeda, W.-H. Wang, B. Hashiguchi, R. Periana, D. J. Szalda, J. T. Muckerman, E. Fujita, *Nat. Chem.* **2012**, *4*, 383 – 388.

[12] A possible explanation for these selectivities is proposed in Schemes S2, S3, and S4 in the Supporting Information.

[13] If the reaction of **3 n** was performed in the absence of base ($NaHCO_3$), **4 n** was obtained in 76 % yield along with 24 % of cyclic ether (1,3-dihydro-1-phenylisobenzofuran), which would be formed by the proton-mediated dehydration of **3 n** via a secondary carbocation intermediate. This result suggests that the role of base is as an acceptor of the proton formed in the initial step of the catalytic mechanism (see Scheme 5).

[14] To study the tolerance of a $C{=}C$ bond, the reaction of **3 a** was examined in the presence of styrene, which is susceptible to hydrogenation. If the reaction of **3 a** (1.0 mmol) was conducted in the presence of **1 a** (1.0 mol %) and styrene (1.0 mmol) under reflux in H_2O for 6 h, **4 a** was obtained in 66 % yield along with recovered styrene (90 %) and ethylbenzene (10 %). This result suggests that the $C{=}C$ bond would be mostly tolerated in the dehydrogenative lactonization catalyzed by **1 a**, although the reaction was slightly slowed.

[15] The reuse of catalyst **1 a** in the dehydrogenative lactonization of **3 i** is also shown in Scheme S1 in the Supporting Information.

Received: August 27, 2013
Revised: October 15, 2013