Hydroruthenation triggered catalytic conversion of dialdehydes and keto aldehydes to lactones†

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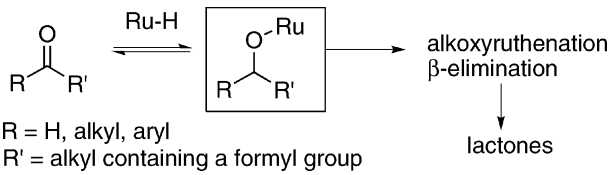
Lactonization of dialdehydes and keto aldehydes was effectively catalyzed by $RuHCl(CO)(PPh_3)_3$. A cascade lactonization sequence accompanied by cross-coupling with enones was also attained.

Lactones are important frameworks found in a variety of biologically active compounds including antibiotics, antifungal compounds, pheromones, lignans, and flavor components.[1] Typically, lactones are prepared by the dehydration reaction of ω-hydroxy carboxylic acids with acid catalyst or stoichiometric coupling reagents such as DCC/DMAP, Mukaiyama–Corey's reagent and Yamaguchi's reagent.[2] On the other hand, the direct conversion of dialdehydes to lactones represents a different approach, which is generally termed as an intramolecular Tishchenko reaction.[2,3] Three decades ago, Yamamoto and coworkers reported that group 8 metal hydrides, such as $RuH_2(PPh_3)_4$, affect Tishchenko dimerization of aldehydes.[4] Inspired by this work, Grigg and coworkers subsequently attained the intramolecular version of the Tishchenko reaction, in which $RhH(CO)(PPh_3)_3$ was used for the conversion of dialdehydes to lactones.[5] Later, the Bosnich group demonstrated the utility of cationic rhodium diphosphine complexes for the dialdehyde–lactone conversion, in which acylrhodium hydride, formed *in situ* by oxidative addition of the starting aldehydes, plays a key role.[6] With a few recent exceptions,[7] the Tishchenko type lactonization reactions have been pursued in a variety of ways other than using transition metal hydrides.[8] During the course of our study on the development of novel catalytic transformations we found that a ruthenium hydride complex, $RuHCl(CO)(PPh_3)_3$, can serve as an excellent catalyst for a variety of atom-economical transformations with aldehydes.[9] This led us to consider the potential of ruthenium hydrides for an hydroruthenation–intramolecular alkoxy-ruthenation sequence (eqn (1)), which would lead to an intramolecular Tishchenko type lactonization reaction. Herein we report that lactonizations of both dialdehydes and keto aldehydes were affected by using $RuHCl(CO)(PPh_3)_3$ as the catalyst. We also report that in the presence of enones cascade lactonization accompanied by cross-coupling with enones is possible.

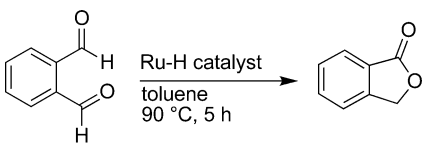


(1)

Using phthalaldehyde (**1a**) as a model compound, we surveyed a variety of ruthenium hydride complexes (Table 1). When a toluene solution of **1a** was treated with $RuHCl(CO)(PPh_3)_3$ (0.5 mol%) at 90 °C for 5 h, 1-(3*H*)-isobenzofuranone (**2a**), the envisaged lactone, was obtained in 94% yield (entry 1). The yield of **2a** became nearly quantitative when 1 mol% of $RuHCl(CO)(PPh_3)_3$ was used (entry 2). Other ruthenium hydride complexes, such as $RuH_2(PPh_3)_4$, $RuH_2(CO)(PPh_3)_3$, and $RuH(NO)(PPh_3)_3$, were found to be less effective in giving **2a** (entries 3–5).

We then examined the generality of the reaction, using a variety of dialdehydes **1a–1d**, **1f–1h**, the results for which are summarized in Table 2. The reaction of 2,3-naphthalene dicarboxaldehyde (**1b**) gave lactone **2b** in good yield (entry 2). The reaction also worked well for the synthesis of the seven-membered ring lactone **2c** (entry 3). In the case of unsymmetrical dialdehyde **1d**, no differentiation of the conjugated and unconjugated formyl groups was observed, thereby giving two products, **2d** and **2d′**, as a 1.1 : 1 mixture (entry 4). Aliphatic dialdehydes **1f**, **1g**, and **1h** also worked well to give the corresponding five to seven membered ring lactones **2f–2h**, the yields are moderate to good (entries 6–8).[10] The catalytic lactonization reaction was also effective for

Table 1 Survey of ruthenium hydride catalysts[a]



1a **2a**

Entry	Ru–H catalyst	mol%	**2a** (%)[b]	**1a** (%)[b]
1	$RuHCl(CO)(PPh_3)_3$	0.5	94	6
2	$RuHCl(CO)(PPh_3)_3$	1.0	99	trace
3	$RuH_2(PPh_3)_4$	0.5	5	95
4	$RuH_2(CO)(PPh_3)_3$	0.5	1	95
5	$RuH(NO)(PPh_3)_3$	0.5	19	76

[a] Conditions: **1a** (0.25 mmol), toluene (1.5 mL), catalyst (0.5 or 1 mol%), 90 °C, 5 h. [b] Yield based on ^1H NMR analysis using $Cl_2CHCHCl_2$ as an internal standard.

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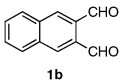
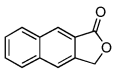
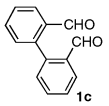
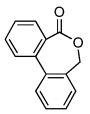
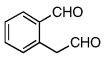
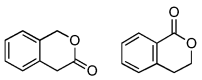
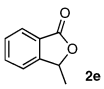
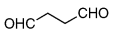
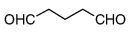
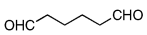
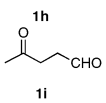
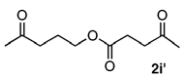
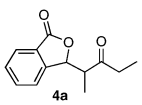
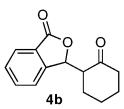
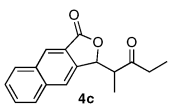
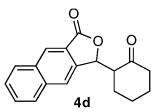
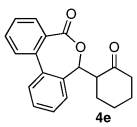
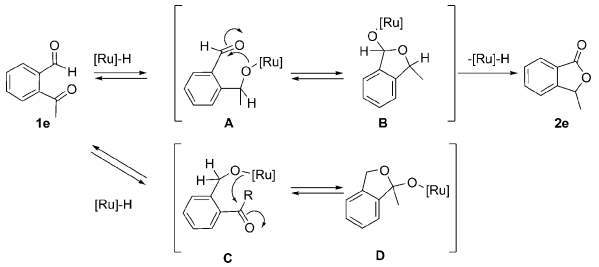
Table 2 Ruthenium hydride catalyzed lactonization of dialdehydes and keto aldehydes

Entry	Aldehydes **1**	Conditions	Lactones **2** and **4**	Yield (%)[a]
1	 **1a**	1 mol% 0.17 M, 90 °C, 5 h	 **2a**	99
2	 **1b**	2 mol% 0.17 M, 110 °C, 5 h	 **2b**	94
3	 **1c**	1 mol% 0.1 M, 110 °C, 5 h	 **2c**	97
4	 **1d**	5 mol% 0.1 M, 90 °C, 5 h	 **2d** **2d'**	99 (1.1 : 1)[b]
5	 **1e**	5 mol% 0.1 M, 120 °C, 40 h	 **2e**	91
6	 **1f**	1 mol% 0.1 M, 110 °C, 5 h	 **2f**	40[c]
7	 **1g**	5 mol% 0.1 M, 90 °C, 10 h	 **2g**	70[c]
8	 **1h**	10 mol% 0.05 M, 110 °C, 20 h	 **2h**	49[c]
9	 **1i**	10 mol% 0.1 M, 120 °C, 40 h	 **2i**	32
			 **2i'**	55
10	**1a**	10 mol% 0.25 M, 90 °C, 5 h ethyl vinyl ketone (**3a**) 5 equiv.	 **4a**	79 (dr = 2 : 1)[b]
11	**1a**	10 mol% 0.25 M, 90 °C, 5 h cyclohexenone (**3b**) 10 equiv.	 **4b**	45 (dr = 4.4 : 1)[b]
12	**1b**	10 mol% 0.25 M, 90 °C, 5 h **3a** 5 equiv.	 **4c**	43 (dr = 1.9 : 1)[b]
13	**1b**	10 mol% 0.25 M, 90 °C, 5 h **3b** 5 equiv.	 **4d**	60 (dr = 3.6 : 1)[b]
14	**1c**	10 mol% 0.25 M, 90 °C, 5 h **3b** 5 equiv.	 **4e**	44 (dr = 2.8 : 1)[b]

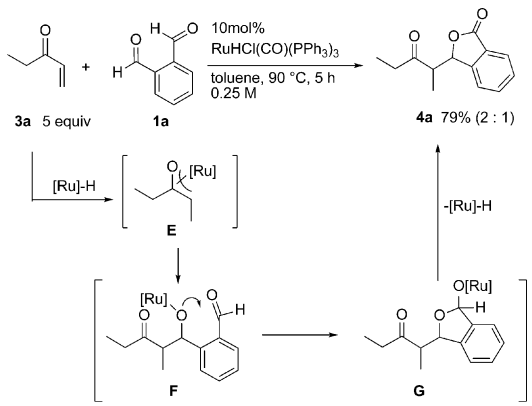
[a] Isolated yield after flash chromatography on SiO_2. [b] The ratio was determined by ^1H NMR. [c] Yield based on ^1H NMR analysis using $Cl_2CHCHCl_2$ as an internal standard.

keto aldehyde **1e**, which gave lactone **2e** having a methyl group at the oxycarbon in 91% yield (entry 5). In the case of aliphatic keto aldehyde **1i**, lactone **2i** was obtained in rather low yield (entry 9), due to a competing Tishchenko reaction leading to ester **2i'**.

A likely reaction mechanism is proposed with an example of a keto aldehyde, **1e** (Scheme 1). The hydroruthenation gives two types of acetal-type Ru complex, **B** and **D**. Ru complex **D**, which arises from hydroruthenation to an aldehyde group,



Scheme 1 Proposed mechanism for lactonization of the keto aldehyde.



Scheme 2 Cascade reaction leading to the substituted lactone.

cannot undergo β-hydride elimination, hence back to **A** *via* **1e**. Eventually, the Ru-complex **B** arising from the hydroruthenation of a ketone carbonyl undergoes cyclization and β-elimination to give lactone **2e**.

As we were curious of the formation and behavior of alkoxyruthenium intermediate **F**, which would be expected to form *via* a Ru-aldol reaction of ethyl vinyl ketone (**3a**) and dialdehyde **1a** (Scheme 2), we examined the RuH-catalyzed cross-coupling reaction of ethyl vinyl ketone (**3a**) with dialdehyde **1a** in detail. To suppress the formation of lactone **2a**, we used enones in excess amounts. Thus, treatment of five molar excess amounts of **3a** with **1a** in the presence of 10 mol% of $RuHCl(CO)(PPh_3)_3$ at 90 °C for 5 h gave the envisaged cross-coupling product 3-(1-methyl-2-oxobutyl)-1(3*H*)-isobenzofuranone (**4a**) in 79% yield (Table 2, entry 10). The cross-coupling reaction of **1a** with 2-cyclohexenone (**3b**) gave the corresponding coupling product **4b** in 45% yield (entry 11). In a similar procedure keto lactones **4c–4e** were obtained (entries 12–14). A proposed reaction mechanism for this cascade reaction is also shown in Scheme 2.[11] Thus, nucleophilic attack of the ruthenium enolate complex[12] to one formyl group of **1a** would give an alkoxyruthenium complex **F**, which is analogous to **A**, then undergoes nucleophilic addition to give **G**. The subsequent β-hydride elimination of **G** would give keto lactone **4a**.

In summary, we have reported that a ruthenium hydride complex, $RuHCl(CO)(PPh_3)_3$, is an efficient catalyst for lactonization of both aromatic and aliphatic dialdehydes. The ruthenium hydride also catalyzed lactonization of keto aldehydes. Cross-coupling reaction of dialdehydes with enones, followed by lactonization was also attained. The intramolecular addition of alkoxy-ruthenium complex to a carbonyl group is considered to be a key step in the lactonization. Ongoing work is being performed to extend the hydroruthenation-based methodology for atom-economical cyclization chemistry.

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Notes and references

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10 The reaction of heptanedial gave a mixture of the envisaged 8-membered lactone (7%) and dimeric cyclic esters (13%).

11 In Bosnich's Rh catalyzed lactonization,[11] it was proposed that the first event is the oxidative addition of an aldehyde to a rhodium complex to generate an acylrhodium hydride complex. Thus, two reaction mechanisms were proposed starting from the complex: (i) intramolecular acylrhodation and reductive elimination, and (ii) hydrorhodation and reductive elimination.

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