$RuHCl(CO)(PPh_3)_3$-Catalyzed Reductive Dimerization of α,β-Unsaturated Aldehydes Leading to α-Hydroxymethyl Ketones

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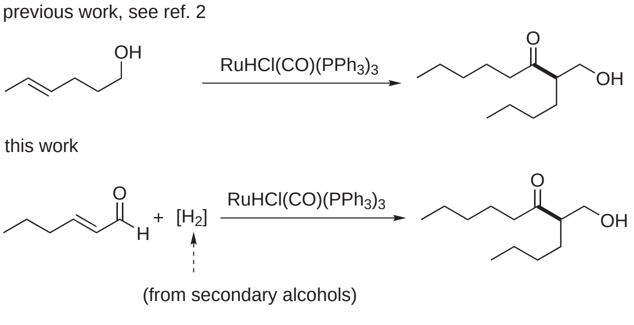
Abstract: The reductive dimerization α,β-unsaturated aldehydes to give saturated ketones was achieved using $RuHCl(CO)(PPh_3)_3$ as a catalyst in the presence of secondary alcohols as hydrogen source. The reaction is likely to proceed via the hydroruthenation of α,β-unsaturated aldehydes followed by aldol reaction of the resultant ruthenium enolates with α,β-unsaturated aldehydes to give unsaturated α-hydroxymethyl ketones, which undergo transfer hydrogenation to give α-hydroxymethyl ketones.

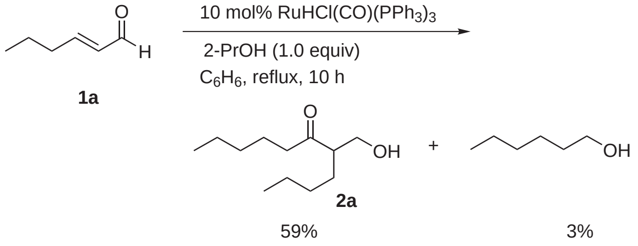
Key words: ruthenium enolates, aldol reaction, α-hydroxymethyl ketones, α,β-unsaturated aldehydes, transfer hydrogenation

Metal-catalyzed coupling reactions have found a tremendous number of applications in organic synthesis.[1] We recently reported unusual dimerization of unsaturated primary alcohols to give α-hydroxymethyl ketones, which was catalyzed by $RuHCl(CO)(PPh_3)_3$ (first equation of Scheme 1).[2] We also found that transfer hydrogenation of unsaturated ketones leading to saturated ketones took place using the same Ru-catalyst and secondary alcohols, such as 2-propanol, as hydrogen source.[3] We became interested in whether the reductive dimerization reaction of α,β-unsaturated aldehydes under the transfer hydrogenation conditions would occur to give the dimerization products or not (second equation of Scheme 1). Herein we report that $RuHCl(CO)(PPh_3)_3$ indeed catalyzes reductive dimerization of α,β-unsaturated aldehydes **1** leading to good to modest yields of α-hydroxymethyl ketones **2**.



Scheme 1 Two types of dimerization reactions leading to α-hydroxymethyl ketones

When a benzene solution of 2-hexenal (**1a**, 0.16 M) and 2-propanol (1.0 equiv) was treated with $RuHCl(CO)(PPh_3)_3$ (10 mol%) at reflux for 10 hours, 2-hydroxymethyl-5-dodecanone (**2a**) was formed in 59% yield (Scheme 2). A small amount of 1-hexanol was formed as a by-product. The use of some other ruthenium complexes, such as $RuHCl(PPh_3)_3$ and $RuH_2(PPh)_4$, under similar conditions was unsuccessful, and resulted in the recovery of **1a** in 92% and 83% yields, respectively.



Scheme 2

The results of the reductive dimerization of a series of α,β-unsaturated aldehydes **1** are summarized in Table 1. Some other secondary alcohols, such as cyclohexanol and 2-octanol, could be employed as a hydrogen source (entries 1 and 2). Crotyl aldehyde (**1b**) underwent dimerization reaction, leading to the hydroxymethyl ketone **2b** in 56% isolated yield (entry 3). Whereas the reaction of cinnamaldehyde (**1c**) in the presence of 1.2 equivalents of 2-propanol gave the corresponding α-hydroxymethyl ketone **2c**, along with small amount of unsaturated hydroxymethyl ketone **3c** (entry 4), the formation of **3c** was suppressed by using a larger amount of 2-propanol (entry 5). No dimerization product was obtained in the reaction of 2-methyl-2-pentanal, (entry 7). The reaction of 2-decenal (**1i**), having a long alkyl chain, gave **2i** in 47% together with 6% yield of unsaturated dimer **3i** (entry 11).

We carried out time-course experiment of the reaction using **1a** as a model substrate, whose results are summarized in Scheme 3. Thus, it was found that **1a** was consumed within 15 minutes, and unsaturated dimer **3a**[4] was formed as a primary product. Then **3a** was converted into saturated dimer **2a** by transfer hydrogenation.[3] After 10 hours, conversion of **3a** to **2a** was complete.

Taking the results into consideration, a possible mechanism for the present reductive dimerization is outlined in Scheme 4. Hydroruthenation of **1a** would give ruthenium enolate **A**,[5] which then undergoes aldol reaction with **1a**.[6,7] β-Elimination from the resulting aldol adduct **B**, followed by transfer hydrogenation of an aldehyde moiety

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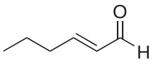
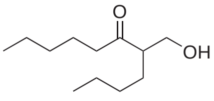
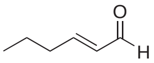
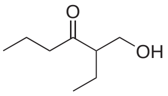
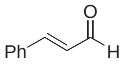
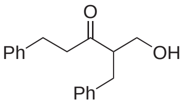
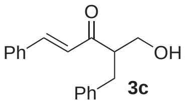
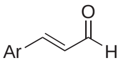
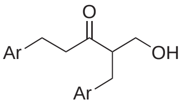
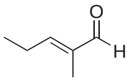
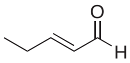
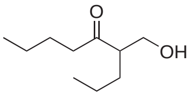
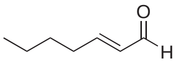
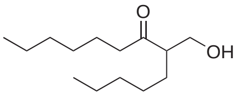
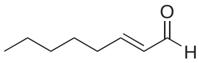
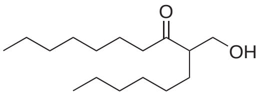
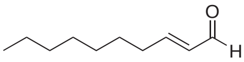
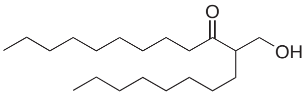
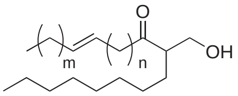
Table 1 Reductive Dimerization of α,β-Unsaturated Aldehydes **1** to 2-Hydroxymethyl Ketones **2** Catalyzed by $RuHCl(CO)(PPh_3)_3$[a]

Entry	Substrate	Alcohol (equiv)	Product		Yield (%)[b]
1 2	 **1a**	Cyclohexanol (1.4) 2-Octanol (1.2)	 **2a**		64 62
3	 **1b**	2-PrOH (1.2)	 **2b**		56
4	 **1c**	2-PrOH (1.2)	 **2c**	 **3c**	
			49	5	
5	**1c**	2-PrOH (2.0)	65	<1	
6	 **1d** Ar = *p*-MePh	2-PrOH (2.0)	 **2d**		53
7	 **1e**	2-PrOH (1.3)	Not formed[c]		
8	 **1f**	2-PrOH (2.0)	 **2f**		57
9	 **1g**	2-PrOH (2.0)	 **2g**		55
10	 **1h**	2-PrOH (2.0)	 **2h**		55
11	 **1i**	2-PrOH (1.4)	 **2i**		47
			 **3i**	(m + n = 6)	6

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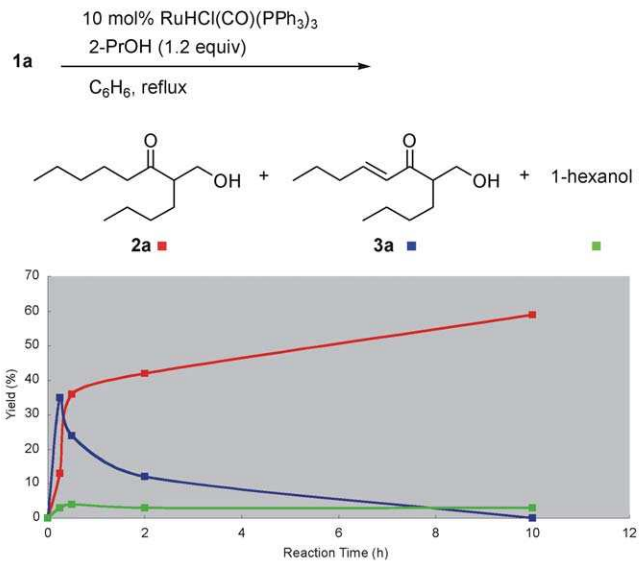
[a] General conditions: substrate (1 mmol), alcohol (1.2–2.0 mmol), $RuHCl(CO)(PPh_3)_3$ (10 mol%), C_6H_6 (6 mL), reflux, 10 h.

[b] Isolated yields. In all cases, sat. alcohols were formed as by-product. For examples, entry 3: 5%, entry 5: 11%, entry 9: 6%.

[c] Unreacted **1e**, 2-methylpentanal, and 2-methyl-1-pentanol were obtained as a mixture.



Scheme 3 Time course of the reaction of **1a**

gives unsaturated dimer **3a**. The second transfer hydrogenation of **3a** then takes place to give α-hydroxymethyl ketone **2a**.

In conclusion, the reductive dimerization of α,β-unsaturated aldehydes **1** to α-hydroxymethyl ketones **2** is catalyzed effectively by $RuHCl(CO)(PPh_3)_3$ in the presence of secondary alcohols as hydrogen source.[8] The reaction proceeds via aldol reaction of ruthenium enolates with α,β-unsaturated aldehydes, followed by transfer hydrogenation to give unsaturated dimer **3** as a primary product. Selective transfer hydrogenation of the C=C bond gave saturated dimer **2** as the final product. Extension of the present work to cross-coupling reactions is now being pursued in our laboratory and will be reported in due course.

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(4) After 15 min, **3a** contained ca. 17% of double-bond isomers.

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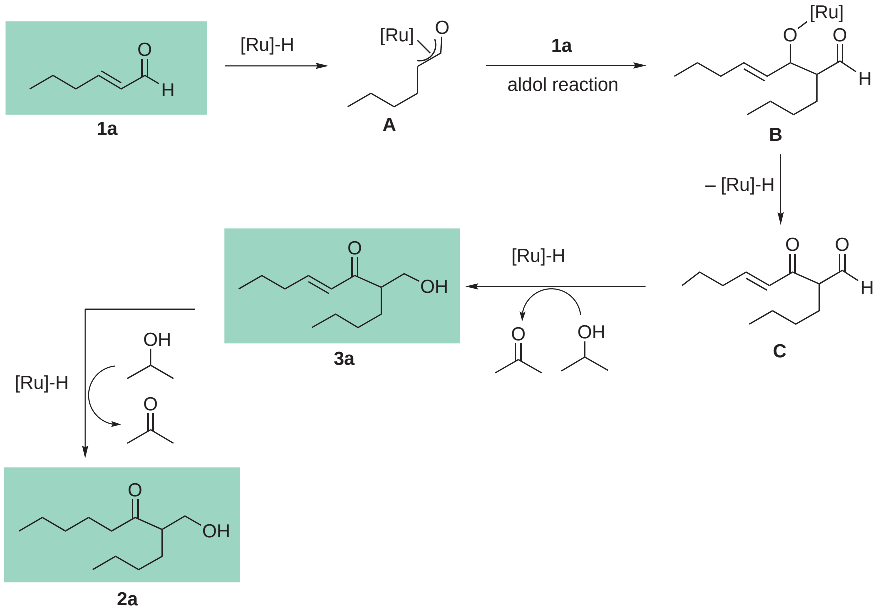

Scheme 4 Possible mechanism of reductive dimerization

(7) For reviews on catalytic reductive aldol coupling, see: (a) Motherwell, W. B. *Pure Appl. Chem.* **2002**, *74*, 135. (b) Huddleston, R. R.; Krische, M. J. *Synlett* **2003**, 12. (c) Jang, H.-Y.; Krische, M. J. *Eur. J. Org. Chem.* **2004**, 3953. (d) Jang, H.-Y.; Krische, M. J. *Acc. Chem. Res.* **2004**, *37*, 653. (e) Chiu, P. *Synthesis* **2004**, 2210.

(8) **General Procedure for the $RuHCl(CO)(PPh_3)_3$-Catalyzed Reductive Dimerization of α,β-Unsaturated Aldehyde.**
A mixture of **1a** (103 mg, 1.03 mmol), 2-PrOH (63 mg, 1.05 mmol), and $RuHCl(CO)(PPh_3)_3$ (96.0 mg, 0.1 mmol) in benzene (6 mL) was stirred at reflux for 10 h under an atmosphere of N_2. Purification by silica gel column chromatography and preparative HPLC equipped with GCP column gave α-hydroxymethyl ketone **2a** (59.0 mg, 59%).