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Aldol reaction via in situ olefin migration in water

Mingwen Wang and Chao-Jun Li*

Department of Chemistry, Tulane University, New Orleans, LA 70118, USA

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Abstract—In the presence of a catalytic amount of $RuCl_2(PPh_3)_3$, aldehydes reacted with allyl alcohols to give aldol-type products in water and under an atmosphere of air. © 2002 Elsevier Science Ltd. All rights reserved.

The aldol reaction is one of the most important reactions for forming carbon–carbon bonds. However, under the classical aldol reaction conditions,[1] dimerization, polymerization, and self-condensation also occur. To alleviate such competing processes, an important modification of the classical aldol reaction has been developed by reacting the enol silyl ether with carbonyl compounds in the presence of Lewis acids (the Mukaiyama aldol reaction).[2] Recently, attention has been focused on developing cross-aldol reactions by alternative approaches. Toward this, Trost reported a highly efficient formation of aldol-type products via vanadium-catalyzed coupling of propargyl alcohols with aldehyde.[3] Recent developments also include hydrometalation-aldol[4] and α-C–H activation-aldol reactions of carbonyl compounds.[5] Motherwell developed the Rh- and Ni-catalyzed isomerization of allylic lithium alkoxide to lithium enolate that undergoes further aldol reaction.[6] Grée[7] recently reported the isomerization of allyl alcohol to enol catalyzed by $Fe(CO)_5$ under photolytic conditions, which then reacted with aldehydes to give aldol products (together with other by-products).

Recently, interest has been growing to develop organic reactions in aqueous media.[8] For aqueous aldol-type condensations, Chan developed the tin and zinc-mediated cross-couplings of halo-ketones with aldehydes.[9] Lubineau,[10] Kobayashi,[11] Loh,[12] and others[13] developed the aqueous Mukaiyama-type reactions.

Previously, we reported that in the presence of a catalytic amount of $RuCl_2(PPh_3)_3$ functional groups of homoallyl alcohols and allyl alcohols underwent reshuffling in air and water (Fig. 1, route a).[14] A side product of the isomerization is the formation of a ketone (Fig. 1, route b). The formation of this product was rationalized by the competing process involving the break of the allylic C–H bond (instead of the C–O bond) to form a ruthenium–enol complex,[15] which was then hydrolyzed to give the ketone. We postulated that in the presence of an aldehyde, such a ruthenium–enol complex may be captured.[16] Herein we wish to report the formation of aldol products via a $RuCl_2(PPh_3)_3$-catalyzed cross coupling of allyl alcohols and aldehydes (Scheme 1).

To begin our study, 3-buten-2-ol was stirred with benzaldehyde and a catalytic amount of $RuCl_2(PPh_3)_3$ (3 mol%) in water for 5 h at 110°C (oil bath), no desired product was obtained. The benzaldehyde was found to have been partially oxidized into benzoic acid. No reaction was observed when the solvent was switched to toluene. When the reaction was performed in a 1:4 (volume) mixture of water and toluene, a smooth reac-

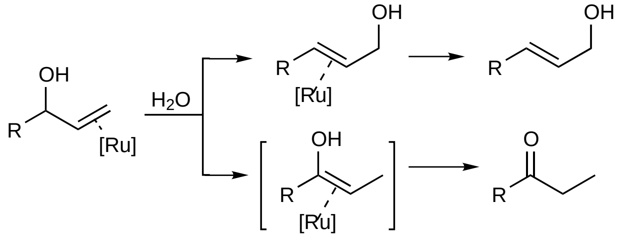
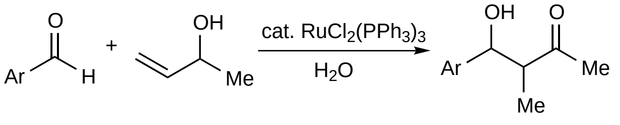


Figure 1.



Scheme 1.

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* Corresponding author.

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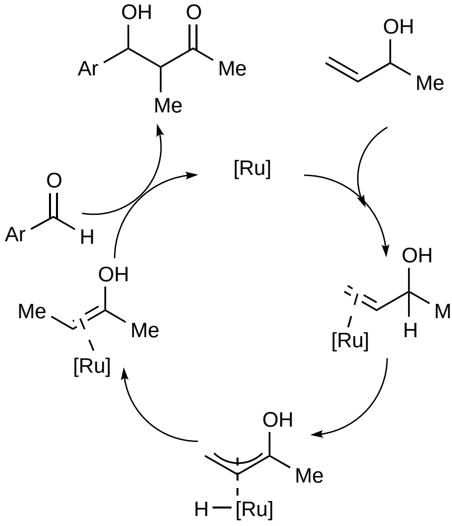

Scheme 2. Tentative mechanism for the ruthenium-catalyzed aldol reaction via olefin migration.

tion occurred to give the desired aldol product (with a *syn*:*anti* ratio of 70:30) in 50% isolated yield. Changing the solvent to 4:1 (water–toluene) further increased the yield (76%) and the *syn*:*anti* ratio (73:27) of the aldol product. The use of water–ethanol (4:1) mixture decreased both the yield (40%) and the diastereoselectivity (*syn*:*anti*=60:40). Subsequently, a variety of aromatic aldehydes were examined under the same reaction conditions. In most cases, the desired aldol product was obtained in good yield. When 3-fluorobenzaldehyde was used, the use of water alone as the solvent provided the desired product in 76% isolated yield. The use of aliphatic aldehydes provided a complicated mixture and efforts are currently underway to improve the reactions with such aldehydes.

A tentative mechanism for the product formation is depicted in Scheme 2. The ruthenium complex isomerizes the allyl alcohol to an enol that is coordinated with the ruthenium catalyst; an in situ reaction between the enol–ruthenium complex with the aldehyde generates the aldol product. The formation of primarily *syn* isomer (Tables 1 and 2) is consistent with previous studies on Mukaiyama aldol reactions in aqueous media.

In conclusion, we have developed an aldol-type reaction via the cross-coupling of aldehyde and allyl alcohols catalyzed by $RuCl_2(PPh_3)_3$ in water. The scope, mechanism, and synthetic applications of the reaction are under investigation. A typical experimental procedure is as follows.

A mixture of aldehyde (1 mmol), 3-buten-2-ol (2.5 mmol) and $RuCl_2(PPh_3)_3$ (0.03 mmol) in water (10 ml) and under an atmosphere of air was stirred at 110°C. After 5 h, the reaction mixture was cooled to room temperature, extracted with ethyl ether, washed with brine and dried over anhydrous Na_2SO_4. The mixture was then concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: hexane/EtOAc) to afford the desired aldol product.

Table 1. Optimization of conditions for aldol reactions between allyl alcohols and aldehydes

Entry	Substrate (R)	Catalyst (3 mol%)	Solvent	Temp. (°C)	Time (h)	Yield (%)[a]	*syn*:*anti*[b]
1	Ph	$RuCl_2(PPh_3)_3$	H_2O	110	5	0	
2	Ph	$RuCl_2(PPh_3)_3$	Toluene	Reflux	5	0	
3	Ph	$RuCl_2(PPh_3)_3$	H_2O–Toluene (1:4)	70	5	Trace	
4	Ph	$RuCl_2(PPh_3)_3$	H_2O–Toluene (1:4)	110	5	50	70/30
5	Ph	$RuCl_2(PPh_3)_3$	H_2O–Toluene (4:1)	110	5	76	73/27
6	Ph	$RuCl_2(PPh_3)_3$+3% $NaHCO_3$	H_2O–Toluene (4:1)	110	5	Trace	
7	Ph	$RuCl_2(PPh_3)_3$	H_2O–EtOH (4:1)	110	5	40	60/40

[a] Isolated yields were referred.
[b] *syn*:*anti* were determined by the ^1H NMR of the product mixture.

Table 2. Aldol-type reaction between allyl alcohols and aldehydes in water

Entry	Substrate (R)	Solvent	Time (h)	Yield (%)[a]	*syn*:*anti*[b]
1	*m*-F–Ph	H_2O	5.5	72	66/34
2	*p*-Cl–Ph	H_2O	5.5	35	60/40
3	*p*-Cl–Ph	H_2O–Toluene (4:1)	5	70	74/26
4	*p*-MeO–Ph	H_2O–Toluene (4:1)	5	68	51/49
5	*p*-Br–Ph	H_2O–Toluene (4:1)	5	73	79/21
6	*p*-Ph–Ph	H_2O–Toluene (4:1)	5	27	67/33
7	2-Naphthyl	H_2O–Toluene (4:1)	5	44	63/37

Reaction conditions: 3% mol $RuCl_2(PPh_3)_3$ at 110°C (oil bath temperature).
[a] Isolated yields were referred.
[b] *syn*:*anti* were determined by the ^1H NMR of the product mixture.

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