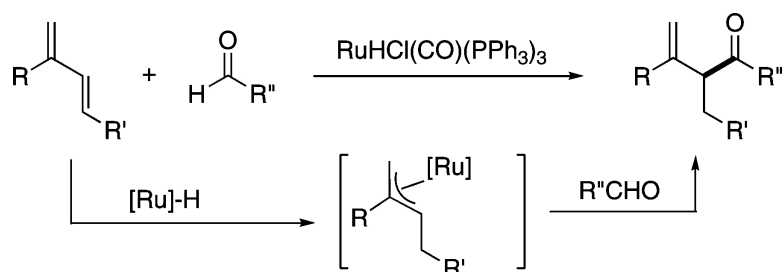


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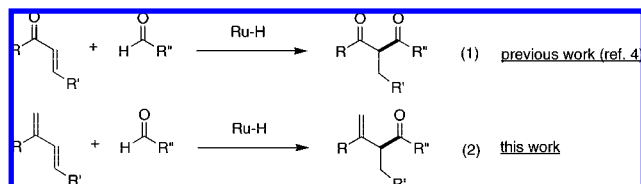
## Ruthenium Hydride-Catalyzed Addition of Aldehydes to Dienes Leading to $\beta,\gamma$ -Unsaturated Ketones

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Transition metal hydrides are involved in a variety of catalytic transformations, and hydrometalation of such species to unsaturated bonds provides intermediates having metal–carbon or heteroatom bonds.<sup>1</sup> Ruthenium hydride catalysts have played a large role in these important transformations.<sup>2,3</sup> We recently reported that the regioselective addition of aldehydes to unsaturated ketones leading to 1,3-diketones can be effectively catalyzed by RuHCl(CO)(PPh<sub>3</sub>)<sub>3</sub> (eq 1).<sup>4</sup> If a similarly regioselective hydroacylation takes place in the reaction between conjugate dienes and aldehydes,  $\beta,\gamma$ -unsaturated ketones would be formed (eq 2). A decade ago, employing Ru(cod)(cot)PPh<sub>3</sub> as a catalyst, Kondo, Mitsudo and co-workers<sup>5</sup> reported cross-condensation of conjugate dienes and aromatic aldehydes. Albeit pioneering efforts, their system suffers a narrow scope, including unavailability of aliphatic aldehydes and harsh reaction conditions with the use of dienes as a solvent. Considering the importance of this transformation and relying on the potential of ruthenium hydride complexes, we embarked on a study to explore an efficient catalytic system on a synthetically useful level. Herein we report that ruthenium hydride, RuHCl(CO)(PPh<sub>3</sub>)<sub>3</sub>,<sup>6</sup> can serve as an efficient catalyst, providing a general method for the synthesis of  $\beta,\gamma$ -unsaturated ketones from 1,3-dienes and aldehydes.



Using the reaction of isoprene (**1a**) and benzaldehyde (**2a**) as a model (Table 1), we surveyed ruthenium hydride catalysts. We were pleased to find that treatment of a toluene solution of **1a** and **2a** with RuHCl(CO)(PPh<sub>3</sub>)<sub>3</sub> (5 mol %) at 90 °C for 24 h gave the desired cross-addition product, 2,3-dimethyl-1-phenyl-3-buten-1-one (**3a**) in 95% yield (entry 3). Other catalysts, such as RuH<sub>2</sub>(CO)(PPh<sub>3</sub>)<sub>3</sub> and RuHCl(PPh<sub>3</sub>)<sub>3</sub>, gave a smaller amount of the desired product **3a** (entries 4 and 5).

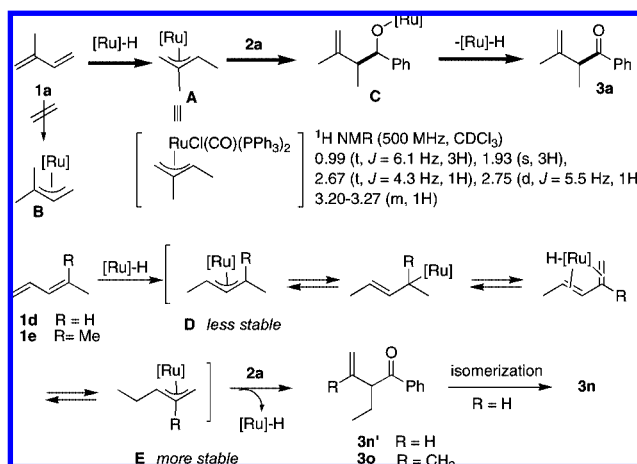
Table 2 illustrates the wide generality and substrate scope of this transformation. Aryl aldehydes, such as *o*- and *p*-tolualdehydes, gave good yields of  $\beta,\gamma$ -unsaturated ketones **3b** and **3c**, respectively (entries 2 and 3). Similarly, *o*-, *m*-, and *p*-methoxybenzaldehydes (**2d–2f**) gave the corresponding ketones **3d–3f** in good yields (entries 4–6). *p*-Fluorobenzaldehyde (**2g**) also reacted with **1a** to give **3g** (entry 7). The reaction was effective for heteroaromatic aldehydes such as **2h** (entry 8) and aliphatic and  $\alpha,\beta$ -unsaturated aldehydes **2i**, **2j**, and **2k** (entries 9–11). The reaction between **2g** and myrcene (**1b**), having one more double bond in the molecule, gave ketone **3l** in 53% yield (entry 12). Since the ruthenium hydride catalyst employed can affect double bond isomerization,<sup>4,6a,b,7</sup> we tested nonconjugate diene **1c**, for which double bond migration would be followed by a cross-coupling reaction. Gratifyingly, **3m**

Table 1. Survey of RuH Catalysts<sup>a</sup>

entry	<b>1a</b> (equiv)	catalyst (mol%)	yield of <b>3a</b> (%) <sup>b</sup>
1	2	RuHCl(CO)(PPh <sub>3</sub> ) <sub>3</sub> (5)	65
2	2	RuHCl(CO)(PPh <sub>3</sub> ) <sub>3</sub> (10)	92
3	4	RuHCl(CO)(PPh <sub>3</sub> ) <sub>3</sub> (5)	95
4	4	RuH <sub>2</sub> (CO)(PPh <sub>3</sub> ) <sub>3</sub> (5)	11
5	4	RuHCl(PPh <sub>3</sub> ) <sub>3</sub> (5)	3

<sup>a</sup> Conditions: **1a** (2 or 4 mmol), **2a** (1 mmol), Ru catalyst (5 or 10 mol%), toluene (6 mL). Reaction was carried out in a screw capped test tube. <sup>b</sup> GC yields using hexadecane as an internal standard.

### Scheme 1. Potential Mechanism



was obtained in good yield via the envisaged alkene-isomerization/dehydrogenative carbonyl addition sequence (entry 13). In the reaction of *trans*-1,3-pentadiene (**1d**(*E*)) with **2a**,  $\alpha,\beta$ -unsaturated ketone **3n** was obtained as an *E/Z* mixture with a ratio of 27/73 (entry 14). Our RuH catalyst system also allows *cis* isomer **1d**(*Z*) to react with **2a** to give **3n** (entry 15).<sup>8</sup> The reaction of 4-methyl-1,3-pentadiene (**1e**) with **2a** gave ketone **3o** in 80% yield as a single product (entry 16). In the case of dialdehyde **2l**, cascade-type cross-condensation took place to give lactone **3p** albeit in moderate yield.

A possible mechanism for the present ruthenium hydride catalyzed reaction is illustrated by the reaction of **1a** with **2a** in Scheme 1. Addition of a ruthenium hydride to **1a** gives  $\pi$ -allyl-ruthenium complex **A**, as confirmed by <sup>1</sup>H NMR spectroscopy.<sup>9,10</sup> No evidence for regioisomeric **B** was found in the NMR study, which may be due to steric considerations. The resulting complex **A** would then undergo reaction with aldehyde **2a** via a six-membered transition state so as to place the bulky Ru-portion of the catalyst at the less hindered methylene carbon. The resulting

**Table 2.** Synthesis of  $\beta,\gamma$ -Unsaturated Ketones by a Ru–H Catalyzed Cross-Coupling Reaction of Dienes with Aldehydes<sup>a</sup>

entry	dienes <b>1</b>	aldehydes <b>2</b>	$\beta,\gamma$ -unsaturated ketones <b>3</b>	yield <sup>b</sup>
1				81%
2				82%
3				78%
4				73%
5				94%
6				70%
7				62%
8				78%
9				89% <sup>c</sup>
10				42% <sup>c</sup>
11				68% <sup>c</sup>
12				53%
13				79% <sup>d</sup>
14				74% <sup>c,e</sup>
15				66% <sup>c,e</sup>
16				80% <sup>d</sup>
17				39% <sup>f</sup> (dr = 62/38)

<sup>a</sup> Conditions: **1** (4 equiv, 2 equiv for entries 4, 5, 6, 12, and 13), **2** (0.5 or 1 mmol), RuHCl(CO)(PPh<sub>3</sub>)<sub>3</sub> (5 mol%), toluene (3 or 6 mL), 90 °C, 24 h. <sup>b</sup> Isolated yield by chromatography on SiO<sub>2</sub>. <sup>c</sup> With 20 mol% of catalyst. <sup>d</sup> With 10 mol% catalyst. <sup>e</sup> NMR yield. <sup>f</sup> With 5 equiv of **1a**. Isobenzofuranone was obtained in 32% yield.

complex **C** would then undergo a  $\beta$ -hydride elimination to give **3a** with liberation of ruthenium hydride. The formation of products **3n** and **3o** in the case of 1,3-pentadiene (**1d** (*E,Z*)) and 4-methyl-1,3-pentadiene (**1e**) (Table 2, entries 14, 15, and 16) may be rationalized by a similar pathway including isomerization of initially

formed  $\pi$ -allylruthenium intermediate **D** to more stable Ru-complex **E**.<sup>11</sup> In a preceding study,<sup>5</sup> however, Kondo et al. proposed a mechanism involving oxidative addition of benzaldehyde to Ru to form a benzoyl(hydride)ruthenium complex,<sup>12</sup> which undergoes the consecutive hydroruthenation of dienes and reductive elimination. To determine whether their mechanism is operative in our RuH system, we carried out a crossover experiment using a mixture of PhCDO (**2a-d**) and *p*-FC<sub>6</sub>H<sub>4</sub>CHO (**2g**) with isoprene **1a**. As the result, we observed nearly equal deuterium scrambling between products **3a-d** and **3g-d**. This result demonstrated that the hydrogen and acyl units that add to the diene do come from different molecules of aldehydes.<sup>13</sup>

In summary, we have developed an efficient cross-addition reaction catalyzed by RuHCl(CO)(PPh<sub>3</sub>)<sub>3</sub>, which provides entry to a wide variety of  $\beta,\gamma$ -unsaturated ketones starting from the corresponding aldehydes and dienes. The detailed mechanism of this reaction as well as further extension of this chemistry is currently under investigation in this laboratory.

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**Supporting Information Available:** Experimental procedure, spectrum data of all products, NMR study. This material is available free of charge via Internet at <http://pubs.acs.org>.

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- (10) For details, see Supporting Information.
- (11) For similar isomerization of  $\pi$ -allylruthenium complexes, see ref 9b.
- (12) In our experiment, no change of chemical shift of carbonyl carbon was observed by NMR analysis when the Ru–H complex was treated with benzaldehyde.
- (13) Concurrent with submission of our work, an aligned study was disclosed by Krische; Shibahara, F.; Bower, J. F.; Krische, M. J. *J. Am. Chem. Soc.* **2008**, *130*, in press (<http://dx.doi.org/10.1021/ja805356j>). We thank Reviewer 1 for proposing this crossover experiment.

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