

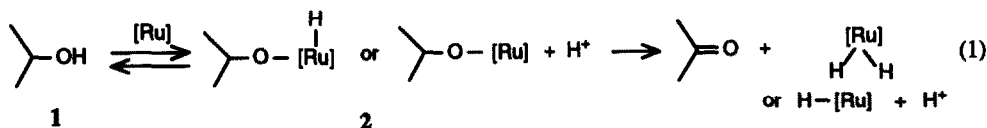
## Ruthenium-Catalyzed Isomerization of Allylic Alcohols to Saturated Ketones

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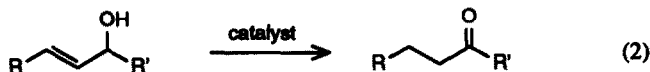
**Abstract.** Highly efficient ruthenium-catalyzed isomerizations of allylic alcohols to ketones have been developed. A dramatic rate enhancement by the presence of a catalytic amount of base was observed in the isomerization catalyzed by either  $\text{RuCl}_2(\text{PPh}_3)_3$  (3) or  $[\text{RuCl}_2(\text{p-cymene})]_2$  (4). Dimetallic catalyst 5, which can itself serve as a base, led to a rapid reaction without the addition of extra base.

We have recently studied ruthenium-catalyzed hydrogen transfer reactions<sup>1</sup> and in this way developed mild procedures for oxidation of alcohols<sup>2</sup> and reduction of ketones<sup>3</sup> and imines.<sup>4</sup> A key step in these reactions is the dehydrogenation of an alcohol (1) via an alkoxy-ruthenium complex 2 and subsequent  $\beta$ -elimination (eq. 1). In an oxidation reaction the alcohol 1 is the substrate whereas in a reduction, alcohol 1

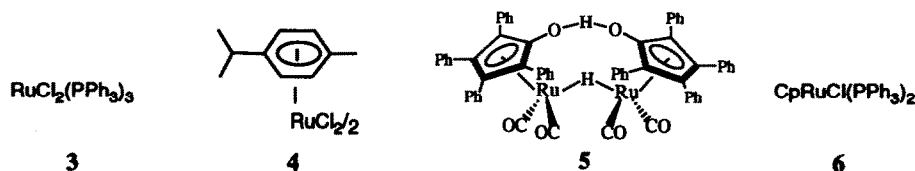


serves as the hydrogen donor. During our studies on these hydrogen transfer reactions, using  $\text{RuCl}_2(\text{PPh}_3)_3$  as catalyst, we observed a dramatic rate enhancement in the presence of a catalytic amount of base.<sup>2b,3,4</sup> This was interpreted as an increased rate of formation of the intermediate alkoxy-ruthenium complex 2.<sup>5</sup>

Transition metal-catalyzed isomerization of an allylic alcohol to a saturated ketone (eq. 2)<sup>6-10</sup> is a reaction that has found limited applicability despite its potential use in organic synthesis. Depending on the metal catalyst employed the reaction can occur via different mechanisms. Although metal-catalyzed double



bond migration to form an enol is the most common pathway,<sup>10</sup> it is likely that a ruthenium-catalyzed isomerization involves intramolecular hydrogen transfer via dehydrogenation of the alcohol (cf. eq. 1) and subsequent transfer of the hydrogens (hydrides) to the double bond. With the aim of developing milder and more efficient methods for isomerization of allylic alcohols to ketones, we decided to investigate the effect of base on the ruthenium-catalyzed reaction. In this study four different catalysts, 3, 4, 5, and 6, have been employed and for the first two a dramatic rate-enhancement was observed upon addition of a catalytic amount of base.

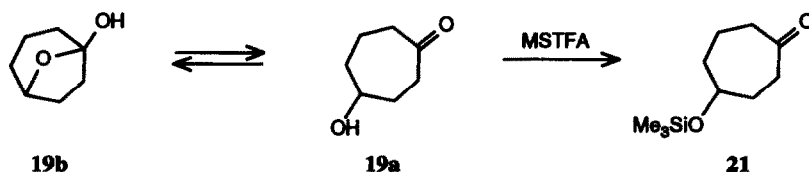


The ruthenium-catalyzed reaction of 1-octen-3-ol (**7**) in tetrahydrofuran (THF) at 65 °C employing 1 mol% of  $\text{RuCl}_2(\text{PPh}_3)_3$  (**3**) as catalyst occurred at a moderate rate with 17 % conversion to saturated ketone after 3h (Table 1, entry 1). The addition of a catalytic amount of  $\text{K}_2\text{CO}_3$  (3 mol%) resulted in a dramatic rate enhancement of the reaction and after 20 min there was a 94 % yield of the saturated ketone (entry 2). Some other catalysts were also tested. For example, *p*-cymene complex **4**<sup>11</sup> (1 mol%) in the presence of  $\text{K}_2\text{CO}_3$  (3 mol%) afforded ketone **4** in quantitative yield after 3 h.

Catalyst **5** has recently attracted attention in hydrogen transfer reactions.<sup>1,12,13</sup> This dimetallic complex is in equilibrium with two mono-metallic species and one of these has a negatively charged oxygen. This alkoxide can act as a base, thus promoting formation of a ruthenium alkoxide. Indeed, using only 0.2 mol% of **5** as catalyst, a very rapid isomerization occurred (Table 1, entry 4), which was complete within 30 min!

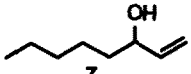
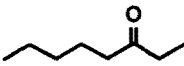
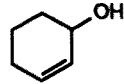






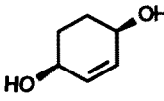



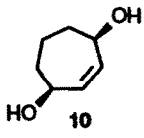
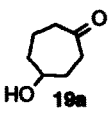
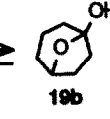
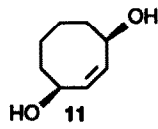
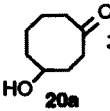
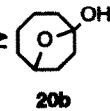
Recently, catalyst **6** with  $\text{Et}_3\text{NHPF}_6$  was used for the rearrangement of allylic alcohols to ketones.<sup>7</sup> For comparison, catalyst **6** was tested under reaction conditions similar to those employed for **3**, **4** and **5** (1 mol%, 65 °C) in the presence of either  $\text{K}_2\text{CO}_3$  or  $\text{Et}_3\text{NHPF}_6$ . As shown in Table 1 (entry 6 and 7), catalyst **6** is considerably slower in both cases.

The ruthenium-catalyzed rearrangements were tested for a number of other substrates (Table 1). In all cases tried there was a rate enhancement by  $\text{K}_2\text{CO}_3$  when **3** or **4** were employed as catalysts. It was of interest to study the isomerization of *meso*-2-alken-1,4-diols to 4-hydroxyketones because of its potential use in asymmetric synthesis.<sup>14</sup> 2-Cyclohexen-1,4-diol (**9**),<sup>15</sup> in the presence of catalyst **5**, produced a mixture of hydroxyketone **16**, unsaturated hydroxyketone **17**, and diol **18** (Table 1, entry 11). The lack of selectivity with this catalyst is due to competing hydrogen transfer to the keto group of the product. When the corresponding reaction was performed with 2-cyclohepten-1,4-diol (**10**)<sup>15</sup> a more selective reaction occurred (entries 12 - 14). Thus, isomerization of **10** with catalyst **3** in the presence of base afforded, in moderate yield, 4-hydroxycycloheptanone (**19a**), in equilibrium with its cyclic hemiacetal **19b**.<sup>16</sup> Neither diol nor unsaturated ketone were detected. When **5** was employed as catalyst a highly efficient and selective reaction occurred, and **19a** (in equilibrium with **19b**) was obtained in 95% isolated yield. Treatment of the equilibrium mixture of **19a** and **19b** with *N*-methyl-*N*-(trimethylsilyl)trifluoroacetamide (MSTFA) afforded ketosilyl ether **21**, which was isolated and characterized.



2-Cycloocten-1,4-diol (**11**)<sup>15</sup> also underwent a highly selective ruthenium-catalyzed reaction to give **20** in good yield (Table 1, entries 15 and 16). Again, the hydroxyketone (**20a**) is in equilibrium with its cyclic

**Table 1.** Ruthenium-Catalyzed Isomerization of Allylic Alcohols<sup>a</sup>

entry	substrate	catalyst	Catalyst concentration (mol %)	time (h)	product	% yield <sup>c</sup>
1		<b>3</b>	1	3		17
2		<b>3</b> + K <sub>2</sub> CO <sub>3</sub>	1	0.33		94
3		<b>4</b> + K <sub>2</sub> CO <sub>3</sub>	1	3		99
4		<b>5</b>	0.2	0.5		99
5		<b>5</b>	0.4	0.33		97
6		<b>6</b> + K <sub>2</sub> CO <sub>3</sub>	1	5		42
7		<b>6</b> + Et <sub>3</sub> NHPF <sub>6</sub>	1	5		20
8		<b>4</b> + K <sub>2</sub> CO <sub>3</sub>	1	7	 	85
9		<b>5</b>	0.5	7		88
10		<b>6</b> + Et <sub>3</sub> NHPF <sub>6</sub> <sup>b</sup>	5	24	 :  : 	77
11		<b>5</b>	0.5	15	  	47 <sup>d</sup>
					8 : 46 : 46	
12		<b>3</b> + K <sub>2</sub> CO <sub>3</sub>	1	6.5	 ⇌ 	65 <sup>d</sup>
13		<b>5</b>	0.5	1.5		95 <sup>d</sup>
14		<b>6</b> + Et <sub>3</sub> NHPF <sub>6</sub> <sup>b</sup>	5	25		72
15		<b>3</b> + K <sub>2</sub> CO <sub>3</sub>	1	3	 ⇌ 	82 <sup>d</sup>
16		<b>5</b>	0.5	1.5		84 <sup>d</sup>

a. Unless otherwise noted the reactions were performed on a 1.0 mmol scale in THF at 65 °C in the presence of the ruthenium catalyst. b. The reaction was performed in dioxane at 100 °C. c. Unless otherwise noted the yield was determined by gas chromatography using n-dodecane as internal standard. d. isolated yield.

hemiacetal (**20b**). In this reaction, catalyst **3** (with K<sub>2</sub>CO<sub>3</sub>) and catalyst **5** gave comparable results with the latter catalyst being slightly faster.

The present study shows that there is a dramatic rate enhancement by a catalytic amount of base (K<sub>2</sub>CO<sub>3</sub>) in the RuCl<sub>2</sub>(PPh<sub>3</sub>)<sub>3</sub>-catalyzed isomerization of allylic alcohols to saturated ketones. Without base the reaction is more than 50 times slower (Table 1, entries 1 and 2). In a previous study<sup>6a</sup> a temperature of 110 °C in neat allylic alcohol **7** was required to obtain a comparable rate to that obtained in a 1M THF solution of **7**

at 65 °C when base is used (entry 2, Table 1). In addition, this study shows that the catalyst of choice varies with the substrate. For substrates **7** and **11**, complexes **3** (with  $K_2CO_3$ ) and **5** gave comparable results with the latter being slightly faster. The former is commercially available<sup>17</sup> and is therefore recommended for these substrates. For substrate **10** catalyst **5** is preferred. The reaction employing catalyst **6** with  $Et_3NHPF_6$  is slow (entry 7, Table 1) and requires a slightly elevated temperature (100 °C, entries 10 and 14, Table 1) together with a higher molar ratio of the catalyst (5 mol%).<sup>7</sup> However, in spite of this, the higher selectivity obtained in some cases with this catalyst (e.g. entry 10, Table 1), makes it useful for certain substrates.

After the submission of our manuscript a full account on the work by Trost on catalyst **6** and its extension to the  $\eta^5$ -indenyl analogue appeared.<sup>7b</sup> In this paper evidence for an intramolecular 1,3-hydrogen shift is provided, which is consistent with a mechanism involving dehydrogenation of the alcohol to give a coordinated  $\alpha,\beta$ -unsaturated ketone followed by hydride addition to the  $\beta$ -position.

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