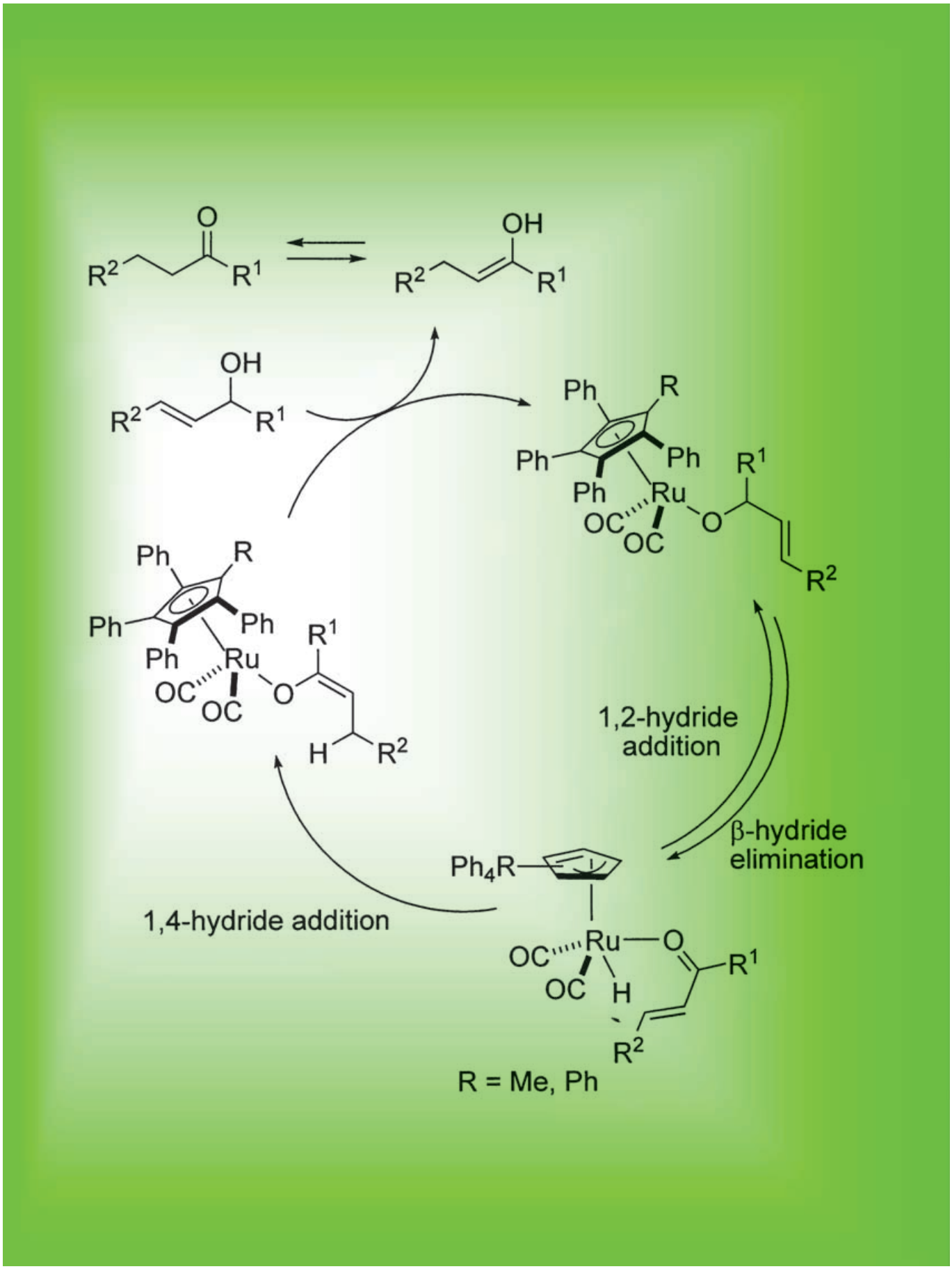


DOI: 10.1002/chem.200500490

Highly Efficient Redox Isomerization of Allylic Alcohols at Ambient Temperature Catalyzed by Novel Ruthenium–Cyclopentadienyl Complexes—New Insight into the Mechanism

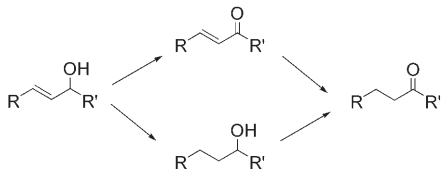
Belén Martín-Matute,*[a] Krisztián Bogár,[a] Michaela Edin,[a] F. Betül Kaynak,[b] and Jan-E. Bäckvall*[a]

Abstract: A range of ruthenium cyclopentadienyl (Cp) complexes have been prepared and used for isomerization of allylic alcohols to the corresponding saturated carbonyl compounds. Complexes bearing CO ligands show higher activity than those with PPh_3 ligands. The isomerization rate is highly affected by the substituents on the Cp ring. Tetra(phenyl)methyl-substituted catalysts rapidly isomerize allylic alcohols under very mild reaction conditions (ambient temperature) with short reaction times. Substituted allylic alcohols have been isomerized by employing Ru–Cp complexes. A study of the isomerization catalyzed by [Ru(Ph_5Cp)$(CO)_2$H] (**14**) indicates that the isomerization catalyzed by ruthenium hydrides partly follows a different mechanism than that of ruthenium halides activated by KO*t*Bu. Furthermore, the lack of ketone exchange when the isomerization was performed in the presence of an unsaturated ketone (1 equiv), different from that obtained by dehydrogenation of the starting allylic alcohol, supports a mechanism in which the isomerization takes place within the coordination sphere of the ruthenium catalyst.

Keywords: allylic compounds · hydrides · isomerization · mechanism elucidation · ruthenium

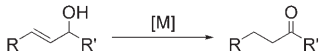
Introduction

The conversion of allylic alcohols into carbonyl compounds conventionally requires two-step sequential oxidation and reduction reactions (Scheme 1).



Scheme 1. Transformation of allylic alcohols to saturated ketones.

Transition-metal complexes allow a one-pot catalytic transformation equivalent to an internal redox process (Scheme 2).[1] This transformation is an atom-economic process, and also avoids the use of costly and usually toxic reagents, especially in the oxidation reactions; this makes it a useful synthetic process that offers applications in the synthesis of natural products and bulk chemicals.



Scheme 2. Transition metal-catalyzed isomerization of allylic alcohols.

Various transition metal complexes of Ru, Rh, Co, Ni, Mo, Ir, and Pt have been already used for this isomerization reaction.[1] However, many of them have restricted scope with regard to the harsh reaction conditions that are required, or to the degree of substitution at the stereocenter (R and R′).

There are several examples of transposition of allylic alcohols catalyzed by ruthenium complexes. For example, $RuCl_3 \cdot xH_2O$ has been employed, but usually gives complicated reaction mixtures.[2] [$RuCl_2(PPh_3)_3$] isomerizes allylic alcohols more reproducibly than $RuCl_3$, but at relatively low

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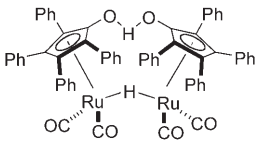
rates and high temperatures (140 °C).[3] Hydride complexes have also been applied. For example, $[RuCl(H)(PPh_3)_3]$ catalyzes the reaction, but is not specific in isomerization of allylic alcohols, since double bonds are isomerized faster.[4] Furthermore, this last system requires high temperatures (110 °C) and the catalysts are air sensitive. An efficient activation of $[RuCl_2(PPh_3)_3]$ has been recently reported by Grée and co-workers.[5] They generated the active species $[RuCl(H)(PPh_3)_3]$ or $[Ru(H)_2(PPh_3)_3]$, in situ by reaction of $[RuCl_2(PPh_3)_3]$ with one or two equivalents of *n*BuLi. $[Ru(acac)_3]$ needs high temperatures (130 °C) and it only works for unsubstituted double bonds.[6] Tetrapropylammonium perruthenate also catalyzes the isomerization in refluxing fluorobenzene.[7]

The first example of Ru^{II}–cyclopentadienyl complexes was reported by Trost and Kulawec in the beginning of the 1990s.[8] They employed $[RuCl(Cp)(PPh_3)_2]$ in combination with $[Et_3NH]PF_6$ in dioxane at 100 °C. However, only allylic primary alcohols or allylic alcohols bearing an unsubstituted vinyl group gave satisfactory results. Trost used 5 mol % of ruthenium catalyst and 10 mol % of $[Et_3NH]PF_6$ catalyst. The activity has been improved by Slugovc et al.,[9] who employed the complex $[Ru(Cp)(PR_3)(MeCN)_2]PF_6$ (1 mol %) in $CDCl_3$ at 57 °C. Unfortunately, as in Trost's case, these catalysts tolerate only a limited substitution pattern on the substrates. Shvo's catalyst (**1**)[10] has also been used in our group.[11] This complex, which is activated at elevated temperature, isomerized allylic alcohols at 65 °C in THF.[11]



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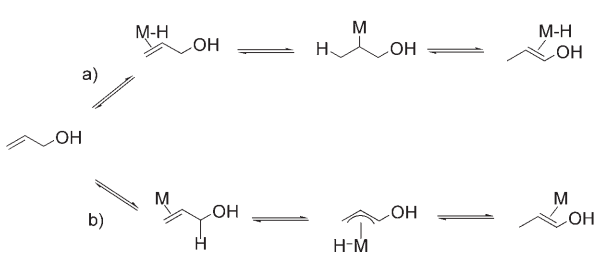
Two main mechanisms have been proposed for the isomerization of allylic alcohols catalyzed by metal complexes.[1] The first one involves alkyl–metal intermediates (path a in Scheme 3). In this case, the catalyst is a metal hydride, either isolated or generated in situ. Insertion of the alkene into the M–H bond, followed by rapid α-CH bond cleavage of the hydrogen atom α to the OH group leads to an enol and regenerates the metal hydride complex. The enol then tautomerizes to the carbonyl derivative. In the second mechanism (path b in Scheme 3), a π-allyl metal hydride complex is formed by coordination of the metal complex (which does not contain a hydride) to the double bond followed by oxidative addition of a C–H single bond.

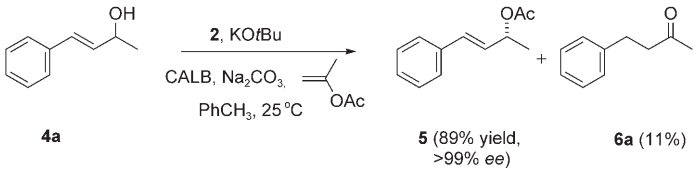


Scheme 3. a) Mechanism via alkyl–metal intermediates. b) Mechanism via π-allyl metal hydride intermediates.

After reductive elimination the coordinated product is produced, which will dissociate to regenerate the starting metal complex.

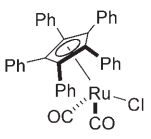
The above presented mechanisms have been proposed in many cases without experimental proof, and none of them assign any role to the oxygen moiety. Furthermore, they cannot explain why in many cases allylic alcohols are isomerized faster than double bonds. There are only few examples in which alternative mechanisms have been proposed that involve coordination of the oxygen moiety.[7,8,11–13] A similar case of isomerization of allylic amines catalyzed by Rh complexes has been reported by Noyori and co-workers, and they propose a mechanism with coordination of the nitrogen atom to the metal center.[14] Similar mechanisms for the isomerization of allylic alcohols in which coordination of the alcohol to the metal complex occurs have received little attention.

Recently, we have developed a highly efficient metal- and enzyme-catalyzed dynamic kinetic resolution (DKR) of alcohols at room temperature, employing an enzyme and ruthenium complex **2** as the catalysts for the kinetic resolution and for the racemization, respectively.[15] When applying the DKR conditions to allylic alcohol **4a**, we obtained the expected enantiopure acetate **5** (89 %) together with 4-phenyl-2-butanone (**6**, 11 %; Scheme 4). When catalyst **3b** was employed, the amount of isomerization product obtained increased to 40 %.



Scheme 4. DKR of allylic alcohol **4a**.

Encouraged by the mild reaction conditions required for the isomerization of allylic alcohols to saturated ketones catalyzed by these ruthenium–cyclopentadienyl complexes (**2**, **3**), we decided to study the rearrangement as a separate process. Here we report the efficient isomerization of allylic alcohols to saturated carbonyl compounds catalyzed by ruthenium–cyclopentadienyl complexes bearing carbon monoxide ligands. The reaction takes place under very mild reaction



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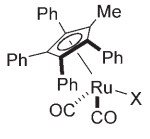


3a X = Cl
3b X = Br

conditions (room temperature) with short reaction times and in almost quantitative yields. To the best of our knowledge, this is one of the few examples of allylic alcohol iso-

merization catalyzed by ruthenium–cyclopentadienyl complexes under such mild reaction conditions. Furthermore, evidence is presented that supports a mechanism in which the alcohol coordinates to the ruthenium center, and after β-hydride elimination a hydride ketone complex is formed. Intramolecular 1,4-addition of the hydride affords a ruthenium enolate. We have prepared a η^5-ruthenium hydride complex, and studied its possible intermediacy in the isomerization reaction. We also provide evidence supporting a mechanism in which the isomerization takes place within the coordination sphere of the Ru atom.

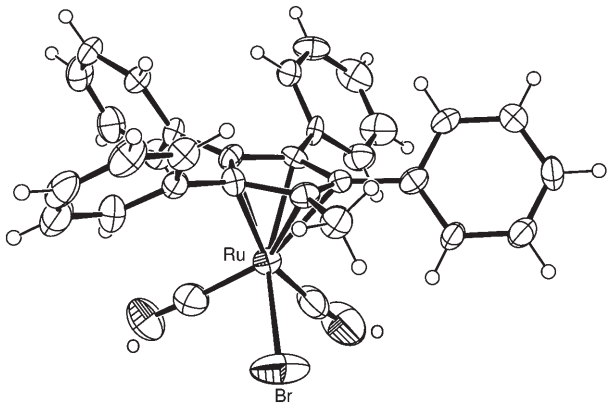
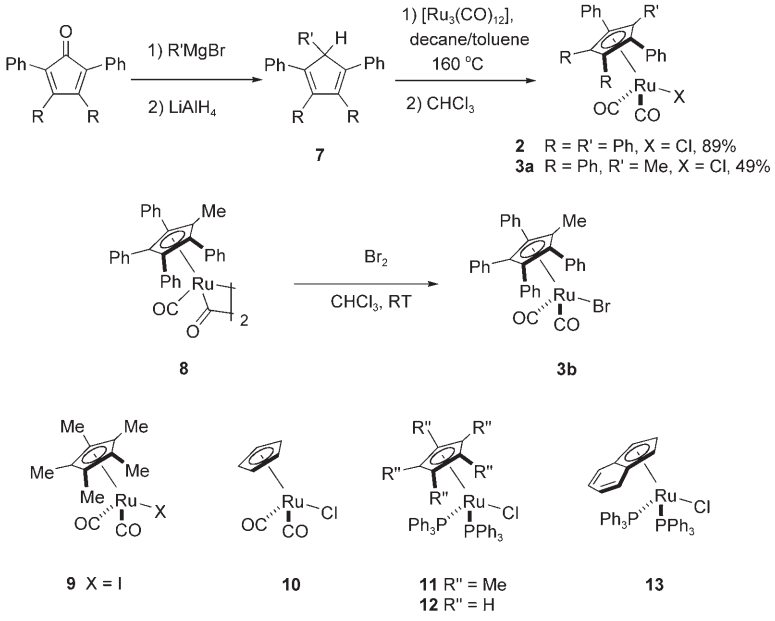


Figure 1. X-ray structure of complex **3b**: Thermal ellipsoids are drawn at 50% probability.[21]

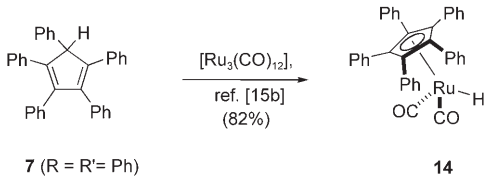
Results and Discussion

Synthesis of the ruthenium complexes: Catalyst **2** was prepared in very high yield by oxidative addition of cyclopentadiene **7** (R = R′ = Ph) to Ru^0, followed by treatment with an excess of chloroform.[15] In a similar way, reaction of cyclopentadiene **7** (R = Ph, R′ = Me) with $[Ru_3(CO)_{12}]$ and $CHCl_3$ afforded catalyst **3a** in 49% yield together with ruthenium dimer **8** (45%).[15,16] Due to the low solubility of this complex, the structure could not be confirmed by NMR spectroscopy. In our previous work we suggested the dimeric structure **8** based on two strong bands at 1960 and 1767 cm^{-1} in the IR spectrum; these bands indicate the presence of nonbridging and bridging CO ligands, respectively.[15] We have now confirmed the structure of complex **8** by oxidative cleavage of the dimeric structure. Thus, dimer **8** was quantitatively transformed to complex **3b** by treatment with an excess of Br_2 at room temperature.[16a] The structure of **3b** was confirmed by X-ray diffraction analysis (Figure 1). Complexes $[Ru(\eta^5\text{-Cp*})(CO)_2I]$ (**9**),[17] $[Ru(\eta^5\text{-Cp})(CO)_2Cl]$ (**10**),[18] $[Ru(\eta^5\text{-Cp*})(PPh_3)_2Cl]$ (**11**),[19] and $[Ru(\eta^5\text{-Cp})(PPh_3)_2Cl]$ (**12**)[20] were prepared as described in the literature (Scheme 5). Indenyl complex **13** is commercially available.



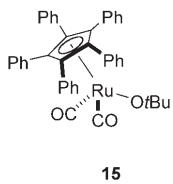
Scheme 5. Ruthenium halide complexes.

Ruthenium hydride $[Ru(\eta^5\text{-}Ph_5Cp)(CO)_2H]$ (**14**) was obtained by oxidative addition of **7** (R = R′ = Ph) to Ru^0 (Scheme 6).[15b]



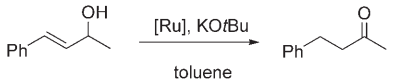
Scheme 6. Ruthenium hydride complex.

Isomerization of 4-phenyl-3-buten-2-ol (4a): With the ruthenium halide catalysts shown in Scheme 5 in hand, we studied the isomerization of allylic alcohol **4a** as a model substrate. We have previously reported the efficient activation of Ru–halide complexes by KO*t*Bu and we identified the formation of Ru–alkoxide complex **15** as the key intermediate.[15] Therefore, the catalysts were activated by using a slight excess of KO*t*Bu in toluene at room temperature before adding the substrate (**4a**).



In sharp contrast to the harsh reaction conditions employed by Trost and Kulawec (5 mol% in dioxane at 100°C),[8] catalyst **3b** (5 mol%) afforded the isomerized product in 96% yield at room temperature in only 1.5 h (entry 1, Table 1). At higher temperatures (45 and 60°C) the catalyst loading can be lowered. Thus, at 45°C the use of 3 mol% of catalyst **3b** afforded the product in 96% yield in only 1 h (Table 1, entry 2). At 60°C the isomerized product is obtained in 98% yield after 10 or 30 min catalyzed by only 2 or 1 mol% of ruthenium catalyst **3a**, respectively (entries 3–4). The use of Na_2CO_3 has no influence on the outcome of the reaction (compare entries 1 and 5), and therefore it was excluded in the subsequent experiments. The isomerization is not significantly affected by the nature of the halide atom, indicating that the active intermediate formed from complexes **3a**,**b** in the catalytic cycle might be the same (compare entries 5 and 6). The more hindered pentaphenyl-substituted catalyst **2** afforded the saturated ketone at room temperature, but 18 h was required to obtain 91% yield (58% yield after 1.5 h; entry 7). In addition, the unsaturated ketone is obtained in 9% (this byproduct is not observed with catalysts **3a**,**b**). The complex $[Ru(Cp^*)(CO)_2I]$ (**9**) also required longer reaction times (entry 8). In this case, the unsaturated ketone was also obtained in 8% yield. The unsubstituted cyclopentadienyl chloride **10** did not catalyze the isomerization at room temperature (entry 9). The substitution of the carbonyl ligands by triphenylphosphine (complex **11**) gave only 26% of the isomerized alcohol after 17 h at room temperature (entry 10). This result shows the importance of CO ligands on the Ru center, and that more electrophilic ruthenium complexes catalyze the isomerization under very mild reaction conditions (compare entries 8 and 10). Similarly to complex **11**, $[Ru(\eta^5\text{-}Cp)(PPh_3)_2Cl]$ (**12**) afforded only 14% yield of **6a** after 17 h at room temperature. However, at 50°C 91% yield was obtained after 17 h (entry 12). The indenyl complex **13** also required longer reaction times (17 h) to give 90% of the product (40% yield (after 1.5 h; entry 13). Despite the fact that 17 h were required for the isomerization catalyzed by indenyl complex **13** activated by KO*t*Bu, it is worth noting the mild reaction conditions (room temperature) used relative to the harsh reaction conditions required (dioxane, 100°C) when the catalyst is activated by an excess of $[Et_3NH]PF_6$.[8]

Table 1. Isomerization of allylic alcohol **4a** catalyzed by various Ru complexes.[a]



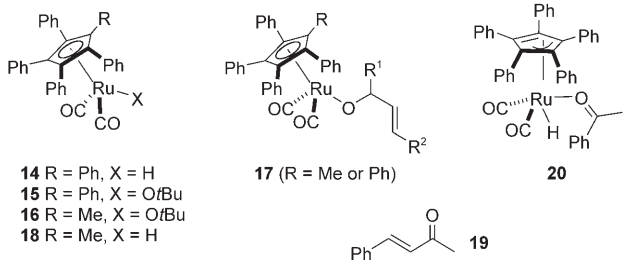
4a **6a**

	Ru [mol%]	KO*t*Bu [mol%]	*T* [°C]	*t* [h]	Yield [%][b]
1[c]	**3b** (5)	7	RT	1.5	96
2[c]	**3b** (3)	6	45	1	96
3	**3a** (2)	2.8	60	0.16	98
4	**3a** (1)	1.4	60	0.5	98
5	**3b** (5)	7	RT	1.5	96
6	**3a** (5)	7	RT	1.5	93
7[d]	**2** (5)	7	RT	1.5	58
8[e]	**9** (5)	7	RT	3	52
9	**10** (5)	7	RT	17	14
10	**11** (5)	7	RT	17	26
11	**12** (5)	7	RT	17	14
12	**12** (5)	7	50	17	91
13[f]	**13** (5)	7	30	1.5	40

[a] Unless otherwise noted, KO*t*Bu (0.5 M in THF) was added to a solution of the Ru catalyst in toluene (substrate concentration: 0.5 M) under an argon atmosphere. The mixture was stirred for 4 min before adding the alcohol. [b] Determined by GC or ^{1}H NMR spectroscopy. [c] One equivalent of Na_2CO_3 was added. [d] 91% yield of **6a** and 9% of benzylidenacetone after 18 h. [e] 92% yield of **6a** and 8% of benzylidenacetone after 24 h. [f] 90% yield after 17 h.

The disadvantages in previously reported isomerizations catalyzed by cyclopentadienyl ruthenium complexes are that, not only are high temperatures required, but also that these catalysts tolerate only a limited substitution pattern on the substrates.[8,9] Only in the case of allylic primary alcohols or allylic alcohols bearing an unsubstituted vinyl group do these procedures give satisfactory results. Therefore, we decided to study the scope and limitations of the isomerization of a variety of allylic alcohols catalyzed by Ru complex **3a**. The results are summarized in Table 2. Similarly to allylic alcohol **4a**, allyl benzyl alcohol **4b** was isomerized at room temperature in only 2.5 h (Table 2, entry 2). Not only aromatic substrates are transformed to the corresponding ketones, but also aliphatic allylic alcohols are isomerized under similar reaction conditions (entry 3). We were pleased to find that more substituted alcohols can be isomerized very efficiently (entries 4 and 5). In the latter case, higher temperatures are required most probably due to steric interaction of the aliphatic chain with the catalyst.[22] Unfortunately, primary allylic alcohol **4f** failed to give any isomerization product at room temperature. Only 22% of the product was obtained at high temperature (entry 6). A plausible explanation is that rather than 1,4-hydride addition to the unsaturated aldehyde intermediate, 1,2-hydride addition takes place faster (vide infra).

Mechanism of the ruthenium-catalyzed isomerization: The first step in the catalytic cycle is the activation of the ruthenium halide complexes **3a**,**b** (or **2**) by KO*t*Bu to give a ruthenium *tert*-butoxide complex **16** (or **15**).[23] In analogy with the color change from yellow to red observed when complex **2** reacts with KO*t*Bu, a mixture of complex **3a** or **3b** and KO*t*Bu in toluene at room temperature gave a strong color change from yellow to dark red after 4 min.



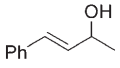
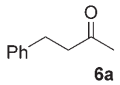
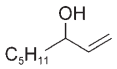
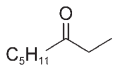
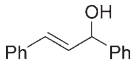
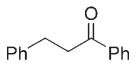
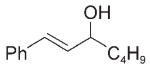
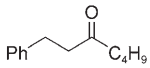
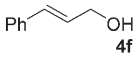
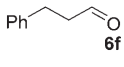
14 R = Ph, X = H
15 R = Ph, X = O*t*Bu
16 R = Me, X = O*t*Bu
18 R = Me, X = H

17 (R = Me or Ph)

20

19

Table 2. Isomerization of a variety of allylic alcohols (**4**) catalyzed by **3a**.[a]

	Substrate	*t* [h]	*T* [°C]	Product	Yield [%][b,c]
1	 **4a**	1.5	RT	 **6a**	96 (96)
2	 **4b**	2.5	RT	 **6b**	99 (94)
3	 **4c**	3	RT	 **6c**	97 (92)
4	 **4d**	2.5	RT	 **6d**	95 (94)
5	 **4e**	2	80	 **6e**	95[d] (94)
6	 **4f**	23	80	 **6f**	22

[a] Unless otherwise noted, KO*t*Bu (7 mol%, 0.5 M in THF) was added to a solution of the Ru catalyst **3a** (5 mol%) in toluene (substrate concentration: 0.5 M) under an argon atmosphere. The mixture was stirred for 4 min before adding the alcohol. [b] Determined by GC or ^{1}H NMR spectroscopy. [c] Isolated yield in parentheses. [d] After 1 h the yield determined by NMR spectroscopy is 87%.

Furthermore, the isomerization is not significantly affected by the nature of the halide atom (vide supra), indicating that the active intermediate formed from complexes **3a**,**b** in the catalytic cycle might be the same. A ligand exchange reaction of **16** (or **15**) with the substrate gives a new alkoxide (**17**), which can undergo β-hydride elimination to produce a ruthenium hydride intermediate **18** (or **14**) and the unsaturated ketone (**19**). We have recently demonstrated that in the racemization of *sec*-alcohols catalyzed by complex **2**, the ruthenium η^5-hydride intermediate **14** is not an abundant species in the catalytic process.[15b] A long induction period of 2.5 hours was observed for the racemization of (*S*)-1-phenylethanol catalyzed by 5 mol% of **14** in the presence of 5 mol% of acetophenone. This result indicated that the reaction of the ruthenium hydride **14** with acetophenone is rather slow. However, once the active species was formed, the racemization proceeded very fast. In sharp contrast, racemization catalyzed by *tert*-butoxide complex **15** (only 1 mol% was employed) occurred in less than 30 min.[15b] Based on these results we proposed β-hydride elimination by means of a $\eta^5 \rightarrow \eta^3$ ring slippage to give hydride ketone complex **20**, in which the ketone stays coordinated to the ruthenium center during the racemization.

To find out whether η^5-ruthenium hydride species (**14** or **18**) are active intermediates in the catalytic isomerization of allylic alcohols, the reaction of **4a** in the presence of ruthenium hydride **14** was studied. In one experiment we studied the isomerization catalyzed by 5 mol% of **14** in the presence of 5 mol% of benzylidenacetone (**19**). We were expecting to observe an induction period due to a slow reaction between ruthenium hydride **14** with **19** to form an active alkoxide intermediate. The reaction was followed by GC, and compared to the reaction catalyzed by complex **3a** activated by KO*t*Bu. As shown in Figure 2, only a slight decrease in the initial rate of the isomerization reaction catalyzed by hydride **14** (in the presence of **19**) was observed. Based on this result a mechanism in which η^5-ruthenium hydride intermediates are formed could not be completely ruled out. However, it is important to note that a mechanism similar to that shown in Scheme 3 (path a) can also be involved when the reaction is catalyzed by ruthenium hydrides. Thus, insertion of the alkene moiety of the allylic alcohol (**4a**) into the Ru–H bond, followed by β-hydride elimination of the hydrogen atom α to the OH group would produce an enol that

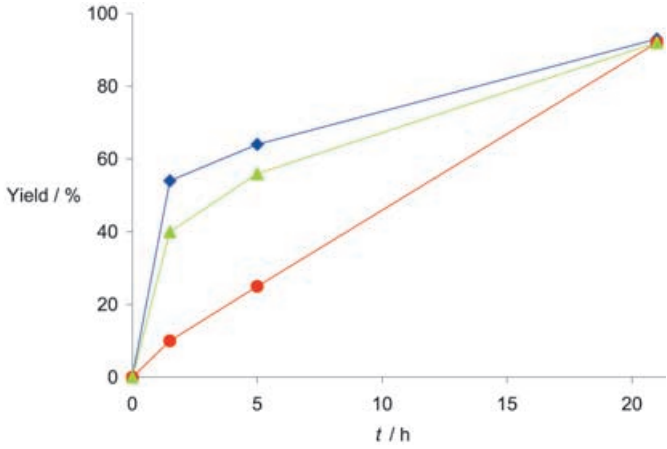
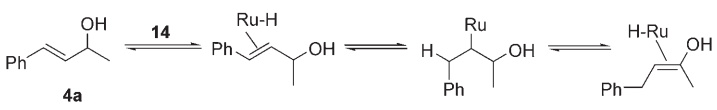


Figure 2. Isomerization of **4a** (0.5 M in toluene) to ketone **6a** catalyzed by: ruthenium chloride **2** (5 mol%) after treatment with KO*t*Bu (◆), ruthenium hydride **14** (5 mol%) in the presence of benzylidenacetone **19** (5 mol%) (▲), and ruthenium hydride **14** (●).

can tautomerize to the saturated ketone (Scheme 7). In this mechanism ruthenium alkoxides are not involved. To prove that such a mechanism also operates, we performed the isomerization of **4a** catalyzed by ruthenium hydride **14** in the absence of ketone **19**. A slower initial rate for this isomerization was observed, but the product was obtained in excellent yield after 21 h (Figure 2). The shape of the curve indi-



Scheme 7. Isomerization mechanism catalyzed by ruthenium hydride complexes.

cates that a more active catalytic species is generated as the reaction proceeds. Furthermore, during the first 3–4 h the reaction mixture remains colorless, and after 4 h it becomes red. The red color is an indication of formation of ruthenium alkoxides (ruthenium *tert*-butoxide complex **15** in toluene is a red solution), and a dark red color is observed for the reactions catalyzed by ruthenium alkoxides.

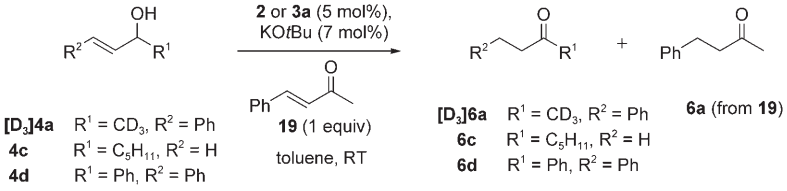
Another approach to probe the intermediacy of η^5-ruthenium hydride complexes (**14** or **18**) is by performing the isomerization of an allylic alcohol catalyzed by ruthenium chloride complexes, activated by KO*t*Bu, in the presence of an unsaturated ketone different from that obtained by oxidation of the starting allylic alcohol. Thus, if the alkoxide from the allylic alcohol (**17**) undergoes β-hydride elimination and a η^5-ruthenium hydride complex (**14** or **18**) is formed, the new unsaturated ketone can now react with the Ru–H moiety and be transformed to the corresponding saturated ketone. If, on the other hand, after β-hydride elimination the substrate stays coordinated to the Ru atom and 1,4-addition of the hydride immediately occurs, the new added unsaturated ketone will remain intact as the reaction proceeds. We decided to study the isomerization of allylic alcohols **4c** and **4d** in the presence of ketone **19** (1 equiv). The reactions were carried out at room temperature in toluene with 5 mol% of catalyst, which was activated by 7 mol% of KO*t*Bu. In the case of catalyst **3a**, after 2.5–3 h, high yields of **6c** and **6d** were obtained and only 6% of the added unsaturated ketone (**19**) had been converted to saturated ketone **6a** (about 6% of the starting allylic alcohols were oxidized to the corresponding unsaturated ketones; Table 3, entries 1 and 2). When catalyst **2** was employed, after 14 h at room temperature, quantitative yield of **6d** was obtained, and ketone **6a** was not detected (Table 3, entry 3). To rule out any effect of disfavored coordination of the added α,β-unsaturated ketone compared to that generated, isomerization of [D_3]**4a** (94% D_3) in the presence of one equivalent of ketone **19** catalyzed by complex **2** was studied. This reaction afforded [D_3]**6a** (84% D_3) in 78% yield. The lower degree of deuterium on the product ([D_3]**6a** (84% D_3)) compared to the starting allylic alcohols ([D_3]**4a** (94% D_3)) indicates that 10% of the added ketone **19** had been reduced to the saturated ketone (Table 3, entry 4).

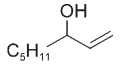
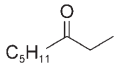
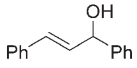
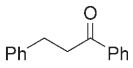
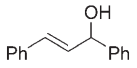
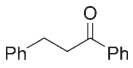
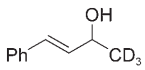
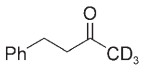
The above results show that at room temperature, the unsaturated ketone obtained from oxidation of the allylic alcohol stays in the coordination sphere of the Ru atom during isomerization, and only exchanges to a minor extent with added free unsaturated ketone. This observation is best explained by the intermediacy of η^3-ruthenium hydride ketone complexes (**21**) after β-hydride elimination from the allylic alcohol. The dissociation of the unsaturated ketone from **21**, leading to exchange, is slow compared to hydride addition (leading to enolate **22**); that is, $k_2 \gg k_1$, considering that the added α,β-unsaturated ketone is in large excess with respect to the α,β-unsaturated ketone generated from the allylic alcohol (Scheme 8).

In the catalytic cycle the ketohydride is obtained from alkoxide complex **17**, which is in turn generated from the precatalyst via *tert*-butoxide complex **15** or **16** (Scheme 9). The hydride in complex **21** can be re-added to the carbonyl group (i.e., 1,2-addition) to form again alkoxide **17**, or alternatively it can be added to the double bond (i.e., 1,4-addition). The addition of the hydride most likely occurs through slippage to the π-coordinated ketone (1,2-addition) or to the π-coordinated alkene (1,4-addition). Insertion of the alkene produces a ruthenium enolate (**22**) that can undergo alkoxide exchange with a molecule of the starting allylic alcohol (**4**) releasing an enol intermediate (**23**) and regenerating alkoxide **17**. The enol then tautomerizes to the carbonyl derivative (**6**) (Scheme 9).

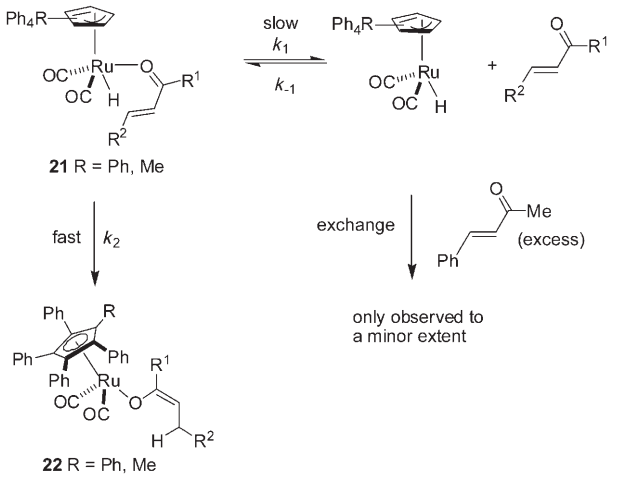
It was of interest estimate the relative rate between 1,2-hydride addition and 1,4-addition, that is, if there is time for reversible 1,2-addition before the irreversible 1,4-addition takes place. To estimate the extent of the 1,2-addition/β-elimination, we studied the redox isomerization of an enantiomerically pure allylic alcohol ((*S*)-**4a**) and measured the enantiopurity of the re-

Table 3. Isomerization of allylic alcohols in the presence of one equivalent of benzylidenacetone (**19**).[a]

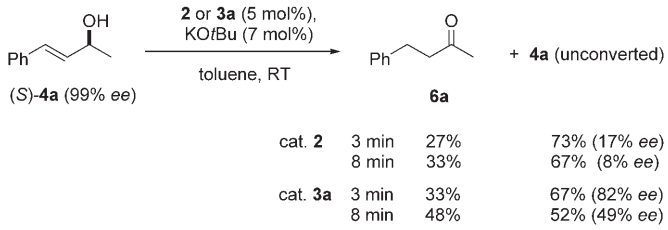


	Substrate	Catalyst	*t* [h]	Product	Yield [%][b]	**6a** [%][b]
1	 **4c**	**3a**	3	 **6c**	94	6
2	 **4d**	**3a**	2.5	 **6d**	86	6
3	 **4d**	**2**	14	 **6d**	100	0
4	 **[D3]4a**	**2**	14	 **[D3]6a**	78 (84% D_3)	10[c]

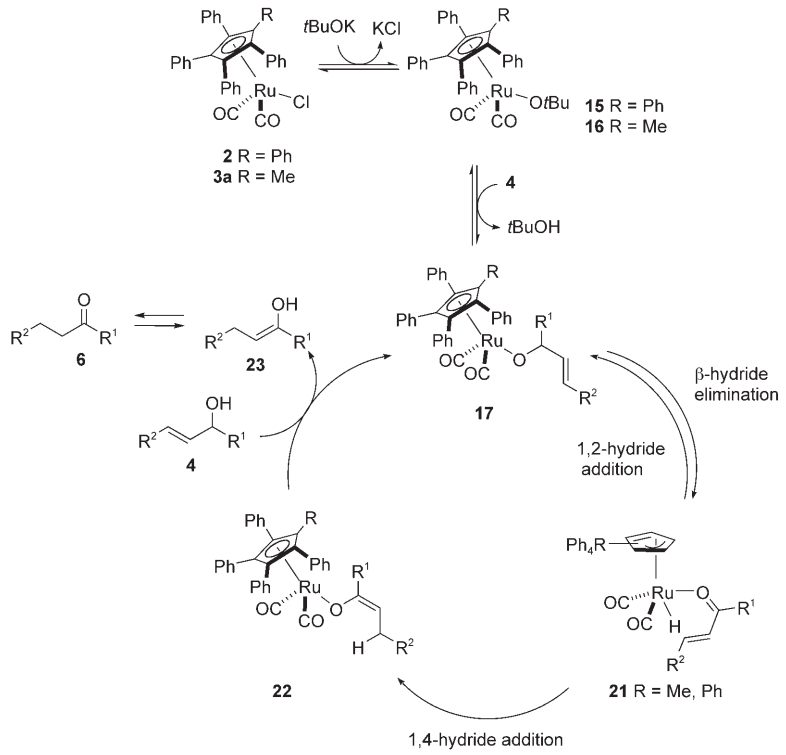
[a] Unless otherwise noted, KO*t*Bu (70 μL, 0.5 M in THF) was added to a solution of the Ru catalyst **3a** or **2** (5 mol%) in toluene (0.5 mL) under an argon atmosphere. The mixture was stirred for 4–6 min before adding a solution of the allylic alcohol and **19** in toluene (0.5 mL). [b] Determined by GC or ^{1}H NMR spectroscopy. [c] Calculated by ^{1}H NMR spectroscopy considering the degree of deuteration of **[D_3]6a**: 94% D_3.



Scheme 8. Hydride addition versus unsaturated ketone dissociation and exchange. R^1 = alkyl, aryl; R^2 = alkyl, aryl.



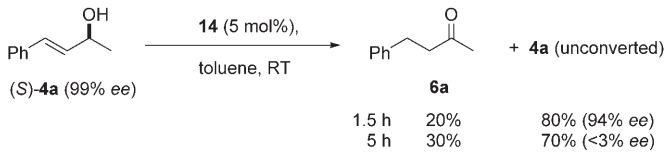
Scheme 10. Redox isomerization of (*S*)-**4a** catalyzed by ruthenium *tert*-butoxide complexes.



Scheme 9. Mechanism of isomerization of allylic alcohols catalyzed by ruthenium cyclopentadienyl complexes. R^1 = alkyl, aryl; R^2 = alkyl, aryl.

maining starting material as the reaction proceeds. As shown in Scheme 10, when catalyst **3a** was employed, after only 8 min 47% of product was obtained, and the *ee* of the remaining starting alcohol had dropped to 49%.[24] When complex **2** was employed as the catalyst, the reaction was slower (32% yield after 8 min), but the *ee* of the remaining alcohol had dropped to 8%.[24] These results indicate that reversible 1,2-addition (i.e., racemization) takes place before the hydride is irreversibly added to the double bond. Furthermore, the rate of 1,2-addition is higher for complex **2** than for complex **3a**, which explains the lower activity of **2** in the isomerization of allylic alcohols. A plausible explanation for the surprisingly slow isomerization of primary allylic alcohols is that with aldehydes, which are more electrophilic species than ketones, the rate of the 1,2-addition might be several orders of magnitude faster than the 1,4-hydride addition that would lead to the product.

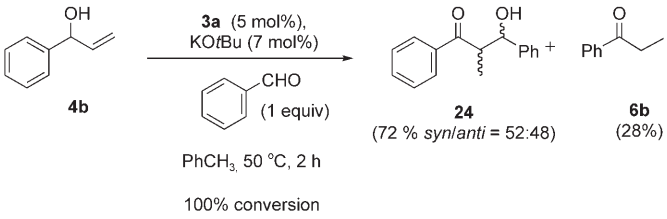
In the discussion above we proposed that the redox isomerization catalyzed by the ruthenium hydride **14** proceeds by means of a different mechanism in the early part of the reaction (Scheme 7). This was based on the color change observed (a change of colorless to red after 3–4 h) and the different rates observed for ruthenium hydride **14** and ruthenium chloride **2**. Now, if the hydride catalyst proceeds through an insertion of the C–C double bond followed by β-elimination according to Scheme 7, this would not involve a ruthenium alkoxide intermediate. To probe whether the mechanism according to Scheme 7 is involved in the early stage of the reaction, we studied the rearrangement of enantiomerically pure starting material (*S*)-**4a** catalyzed by ruthenium hydride **14** (Scheme 11). In the mechanism with insertion of the C–C double bond followed by β-



Scheme 11. Redox isomerization of (*S*)-**4a** catalyzed by ruthenium hydride complex **14**.

elimination (Scheme 7), racemization of the allylic alcohol would not occur during the rearrangement of the allylic alcohol to saturated ketone, whereas in the mechanism via a ruthenium alkoxide complex (Scheme 9) it would. Reaction of (*S*)-**4a** catalyzed by ruthenium hydride **14** gave 20% of the product (**6a**) after 1.5 h and, interestingly, the remaining starting material had not been racemized (94% *ee*) (Scheme 11). However, after 5 h when 30% of **6a** had been obtained, the remaining starting material was racemic. This provides strong support for that the redox isomerization catalyzed by the ruthenium hydride **14** initially follows an insertion (of alkene)/β-elimination pathway (Scheme 7) and that the mechanism switches to an alkoxide mechanism as the reaction proceeds.[25] A plausible explanation for the change of isomerization mechanism is that as the concentration of saturated ketone **6a** builds up, the ruthenium hydride **14** reacts with the product (**6a**) forming a ruthenium alkoxide. A slow reaction of the ruthenium hydride with the ketone to give an alkoxide intermediate (several hours) is in accordance with previous observations.[15b]

Finally, the intermediacy of a ruthenium enolate was probed by isomerizing an allylic alcohol in the presence of an electrophile.[26–28] Thus, when the isomerization of **4b** was performed in the presence of benzaldehyde (1 equiv) at room temperature only 50% of the aldol product **24**[29] (*syn*:*anti* = 83:17) was formed after 14 h. However, after 2 h at 50 °C, **24** was obtained in 72% yield (*syn*:*anti* = 52:48), the remaining product being saturated ketone **6a** (28%) from isomerization of the allylic alcohol (Scheme 12). The

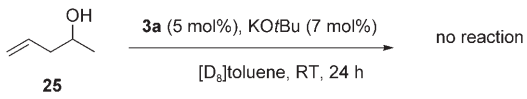


Scheme 12. Tandem isomerization–aldol reaction.

selectivity (*syn*:*anti* ratio) of such an isomerization–aldol tandem process has been discussed in the literature.[28] However, it is important to note that catalysts **2** and **3** are highly efficient in racemizing *sec*-alcohols. Therefore, the aldol product produced is readily epimerized to the *syn*:*anti* mixture obtained, which should be close to the thermodynamic mixture. Indeed, we observed that the *syn*:*anti* ratio changes as the reaction proceeds.[30]

Another advantage of this system is the lack of reactivity of double bonds not bearing an alcohol group at the allylic position. Thus, when homoallylic alcohol **25** was subjected to the reaction conditions no isomerization of the double bond could be observed and after 24 h the starting material remained intact (Scheme 13).

After the completion of this work a communication appeared describing the use of a Ru–Cp* complex with an



Scheme 13. Reaction of homoallylic alcohol **25** with Ru complex **3a** activated by KO*t*Bu.

aminophosphine ligand.[31] This catalyst isomerized allylic alcohols to the corresponding ketone at 30 °C within 1 h.

Conclusion

We have studied the isomerization of allylic alcohols to saturated ketones catalyzed by ruthenium–cyclopentadienyl complexes and demonstrated a higher efficiency with CO ligands than with phosphine ligands coordinated to the ruthenium atom. The use of these complexes in combination with an efficient activation of the ruthenium halide catalysts by KO*t*Bu allows the isomerization of allylic alcohols at ambient temperature with short reaction times. We have studied the mechanism and proven the intermediacy of Ru–alkoxides and Ru–enolates. We also propose the formation of η^3-ruthenium keto hydride complexes. Exchange studies show that the substrate stays coordinated to the ruthenium center through the isomerization mechanism. A study of the isomerization of enantiopure allylic alcohols has shown that the η^3-ruthenium keto hydride intermediate undergoes 1,2-hydride addition several times before irreversible 1,4-hydride addition takes place. Finally, we have found support for a partly different mechanism for the reaction catalyzed by ruthenium hydrides.

Experimental Section

General: All reactions were carried out under dry argon atmosphere in flame-dried glassware. Solvents were purified and dried with standard procedures. Flash chromatography was carried out on 60 Å (35–70 μm) silica gel. ^{1}H and ^{13}C NMR spectra were recorded at 400 or 300 MHz and at 100 or 75 MHz, respectively. Chemical shifts (δ) are reported in ppm, with the residual solvent peak in $CDCl_3$ ($\delta_H = 7.26$ and $\delta_C = 77.00$ ppm) as internal standard, and coupling constants (J) are given in Hz. Enantiomeric excess (*ee*) were determined by analytical gas chromatography employing a CP-Chirasil-Dex CB a chiral capillar column.

Complexes **2**, **3a**, **8**, and **14**, and cyclopentadienes **7** were obtained previously.[15] Allylic alcohols **4b–d** and **4f** are commerically available. Alcohol **4a** was prepared by $NaBH_4$ reduction of (*E*)-4-phenyl-3-buten-2-one as reported in the literature.[32] Enantiopure alcohol (*S*)-**4a** was prepared by CALB-catalyzed kinetic resolution (CALB = *Candida antarctica* lipase B) employing isopropenyl acetate as the acyl donor.[32] Alcohol **4e** was prepared by reaction of *n*BuLi with (*E*)-cinnamaldehyde as reported.[8]

[Ru(η^5-Ph$_4$MeCp)(CO)$_2$Br] (3b): An excess of Br_2 (100 μL) was added to a suspension of dimer **8** (300 mg, 0.277 mmol) in $CHCl_3$ (5 mL) at ambient temperature. After 1.5 h the mixture was washed with a saturated solution of Na_2SO_3 (aq.) (3×5 mL), dried over Na_2CO_3, filtered, and evaporated. Purification by chromatography (SiO_2; pentane/dichloromethane 3:1) afforded complex **3b** as a yellow powder (312 mg, 98%): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.29 (m, 10H), 7.17–7.12 (m, 2H), 7.07–7.03 (m, 4H), 6.99–6.97 (m, 4H), 2.12 ppm (s, 3H); ^{13}C NMR

(100 MHz, $CDCl_3$): $\delta = 196.91$, 132.07, 131.90, 130.00, 129.55, 128.42, 128.38, 128.35, 127.76, 114.39, 105.99, 102.20, 12.46 ppm.

General procedure for the isomerization of allylic alcohols: KO*t*Bu (140 μL; 0.5 M in THF) was added to a solution of complex **3a** (32 mg, 0.05 mmol) in toluene (1 mL) under an argon atmosphere. The mixture was stirred for 4 min before adding a solution of **4a** (148 mg, 1 mmol) in toluene (1 mL). The mixture was stirred at ambient temperature for 1.5 h before adding HCl (1.6 wt%, 0.5 mL). The product was extracted with Et_2O and dried over $MgSO_4$, and the solvent was evaporated. Purification by chromatography (SiO_2; pentane/diethyl ether 97:3) afforded benzylacetone (**6a**) (142 mg, 96%) as a colorless oil. NMR spectra were identical to those obtained from a pure sample of benzylacetone. NMR data of ketones **6b–d** were also compared to those obtained from pure samples. NMR data of ketone **6e** were compared to the reported data.[8]

General procedure for the isomerization of allylic alcohols in the presence of one equivalent of benzylidenacetone (19): KO*t*Bu (70 μL; 0.5 M in THF) was added to a solution of complex **3a** (15 mg, 0.025 mmol) in toluene (0.5 mL) under an argon atmosphere. The mixture was stirred for 4 min. Then, a solution of **4d** (105 mg, 0.5 mmol) and **19** (73 mg, 0.5 mmol) in toluene (0.5 mL) was added. The mixture was stirred at ambient temperature for 2.5 h before adding HCl (1.6 wt%, 0.25 mL). The product was extracted with Et_2O and dried over $MgSO_4$, and the solvent was evaporated. ^{1}H NMR analysis showed 86% of 1,3-diphenyl-1-propanone (**6d**) and 6% of benzylacetone (**6a**). About 6% of *trans*-chalcone was also detected.

4-Phenyl-3-buten-(1-$^2H_3$)-2-ol ([D_3]4a): Benzylideneacetone (4.38 g, 30 mmol), K_2CO_3 (414 mg, 3 mmol), and D_2O (30 mL) were stirred vigorously overnight at 100 °C, then at 120 °C for additional 3 h. The mixture was cooled down to ambient temperature and $NaBH_4$ (571 mg, 15.1 mmol) was added. After 12 h the product was extracted with diethyl ether (3×50 mL), and the combined organic layers were dried over $MgSO_4$. After evaporation of the solvent **[D_3]4a** was obtained as a yellowish oil (4.5 g, 97%, 96% deuterated): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.44$–7.19 (m, 5H), 6.57 (d, $J = 15.7$ Hz, 1H), 6.26 (dd, $J = 15.7$ Hz, 6.3 Hz, 1H), 4.48 (br s, 1H), 1.6–1.8 ppm (m, 0.19H).

Cross-coupling between α-vinylbenzyl alcohol (4b) and benzaldehyde: KO*t*Bu (280 μL; 0.5 M in THF) was added to a solution of complex **3a** (58 mg, 0.1 mmol) in toluene (2 mL) under an argon atmosphere. The mixture was stirred for 4 min and then a solution of **4b** (268 mg, 2 mmol) and benzaldehyde (204 mg, 2 mmol) in toluene (2 mL) was added through a cannula. The mixture was stirred at 50 °C for 2 h before adding HCl (1.6 wt%, 1 mL). The product was extracted with Et_2O and dried over $MgSO_4$, and the solvent was evaporated. ^{1}H NMR analysis showed aldol **24**[29] (72%, *syn*:*anti* = 52:48) and propiophenone (**6b**) (28%): ^{1}H NMR (300 MHz, $CDCl_3$, *anti*-**24**): $\delta = 8.10$–7.23 (m, 10H), 5.00 (dd, $J = 7.9$, 4.0 Hz, 1H), 3.83 (m, 1H), 2.97 (d, $J = 4.0$ Hz, 1H), 1.07 ppm (d, $J = 7.1$ Hz, 3H); the signal at 2.97 ppm disappeared when the sample was shaken with D_2O; ^{1}H NMR (300 MHz, $CDCl_3$, *syn*-**24**): $\delta = 8.10$–7.23 (m, 10H), 5.25 (br d, $J = 3$ Hz, 1H), 3.70 (dq, $J = 7.2$, 3.0 Hz, 1H), 3.6 (br s, 1H), 1.19 ppm (d, $J = 7.2$ Hz, 3H); the signal at 3.6 ppm disappeared when the sample was shaken with D_2O.

Acknowledgements

We are grateful for financial support from the Swedish Research Council, the Swedish Foundation for Strategic Research, the Ministerio de Educación y Ciencia of Spain (B.M.-M.), and the Scientific and Technical Research Council of Turkey (F.B.K).

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Received: May 2, 2005
Published online: July 19, 2005

