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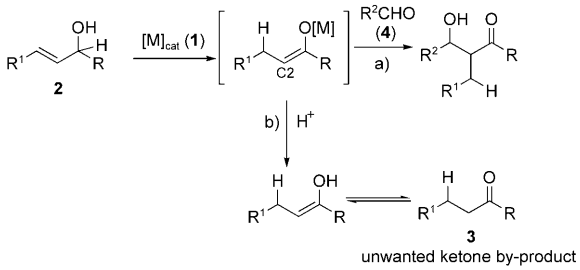
Efficient Synthesis of β-Hydroxy Ketones from Allylic Alcohols by Catalytic Formation of Ruthenium Enolates

Agnieszka Bartoszewicz, Madeleine Livendahl, and Belén Martín-Matute*[a]

Transition-metal complexes **1** catalyze the transformation of allylic alcohols **2** into enols (enolates) (Scheme 1).[1a–c] This internal redox process avoids the use of stoichiometric amounts of oxidizing and reducing agents. In the presence of aldehydes, the in situ generated enolates can be trapped and form important β-hydroxy ketones (aldols) (Scheme 1a).



Scheme 1. a) Formation of aldols from allylic alcohols using a catalytic amount of a transition metal complex. b) Unwanted isomerization pathway.

This transformation is important not only because of the new C–C bond which is formed, but also because two new stereogenic centers are created. Furthermore, the formation of metal enolates via isomerization of allylic alcohols overcomes some of the limitations of the classical approaches. For example, stoichiometric amounts of strong bases or stoichiometric formation of enol derivatives are not necessary, self-condensation products are not produced, and the regioselectivity can be controlled.

The coupling of allylic alcohols with aldehydes has already been performed with some success.[1b,2–4] However, a major problem has been the efficiency of the reaction due to the formation of unwanted ketone by-products (**3**, Scheme 2b) and a low *syn*/*anti* diastereoselectivity. Li et al. used $[Ru(PPh_3)_3Cl_2]$ (**1a**) in toluene/H_2O mixtures at 100 °C to obtain aldols in moderate yields (27–72 %).[2a] When they used aromatic allylic alcohols, such as α-vinylbenzyl alcohol (**2a**),[2b] propiophenone (**3a**) became the major product. The yield of the aldol products dramatically increased in the presence of $In(OAc)_3$.[2b] They also found that in an ionic liquid, the reactions proceeded well at 90 °C.[2c–d] Grée et al. employed $[Ru(PPh_3)_3HCl]$ to produce aldols in up to 72 % yield and in short reaction times (< 2 h).[3a] However, under such conditions, ketones **3** were formed (5–52 %). They have also used Fe and Ni complexes.[3b–e] In the former case, small amounts of regioisomeric aldols were produced. Better results were obtained with Ni complexes and Mg salts as co-catalysts; aldol products were formed in high yields together with small amounts of ketones **3** (2–15 %).

As part of our ongoing research, we decided to search for a ruthenium complex that would perform the isomerization–aldol domino process with the highest possible atom economy. Thus, we aimed to find a ruthenium catalyst that could completely suppress the formation of unwanted ketones **3** while yielding aldol products in quantitative yields, and ideally, under very mild reaction conditions. We report here the most efficient ruthenium-catalyzed transformation of allylic alcohols into aldols, where the formation of unwanted by-products is completely suppressed and aldol products are formed in up to 99 % yield at ambient temperature. We also provide evidence for a mechanism via coordinated alkoxide and coordinated α,β-unsaturated ketone that accounts for the diastereoselectivity obtained.

Ru–halide complexes are the catalysts of choice in many transformations involving hydrogen transfer.[1] In the early 90s, a break-through came with the discovery by Bäckvall et al. of the dramatic acceleration effect (10^3–10^4 fold) induced by the addition of a base (KOH) to a transfer hydrogenation reaction of ketones catalyzed by $[Ru(PPh_3)_3Cl_2]$ (**1a**).[5] Other bases (K_2CO_3, RLi, ROK)[2a] to activate metal–halide complexes can be used. Changing the base

[a] A. Bartoszewicz, M. Livendahl, Dr. B. Martín-Matute
Department of Organic Chemistry, Arrhenius Laboratory
Stockholm University (Sweden)
Fax: (+46) 8-15-4908
E-mail: belen@organ.su.se

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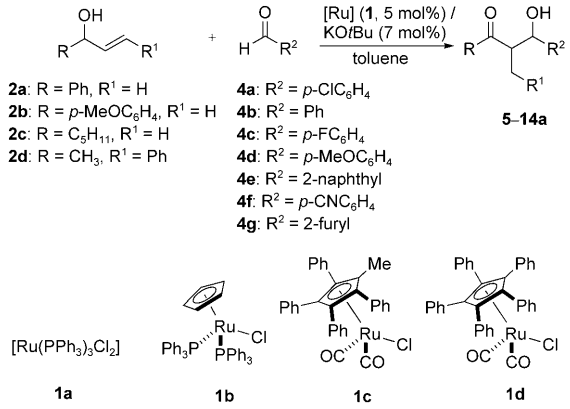
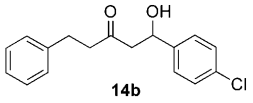
used to activate the complex can result in a complete change of the reactivity during catalysis. In particular, KO*t*Bu has given excellent results,[6] and in one case, a complex with structure of $L_nRuOtBu$ was characterized as a catalytic intermediate.[6d–e]

We reasoned that the activity of a variety of Ru–Cl complexes in the coupling reaction of allylic alcohols with aldehydes could be enhanced by the use of KO*t*Bu. Thus, we studied the Ru-catalyzed couplings between α-vinylbenzyl alcohol (**2a**) and *p*-chlorobenzaldehyde (**4a**) using commercially available ruthenium complexes $[Ru(PPh_3)_3Cl_2]$ (**1a**) and $[\eta^5\text{-}CpRu(PPh_3)_2Cl]$ (**1b**) activated by a catalytic amount of KO*t*Bu (Scheme 2). Unfortunately, neither catalyst **1a** nor **1b** gave any coupling product at ambient temperature. Instead, isomerization of α-vinylbenzyl alcohol (**2a**) to propiophenone (**3a**, Scheme 2b, R¹ = H, R = Ph) was observed in only 3–5 h. Upon heating at 50 °C, **1a** and **1b** afforded aldol **5** in 22–34 % together with ketone **3a** in about 40 % yield. We decided to turn our attention to other Ru complexes. We had used Ru complex **1c** $[\eta^5\text{-}(Ph_4MeCp)Ru(CO)_2Cl]$ before in the coupling of allylic alcohol **2a** with benzaldehyde (**4b**).[7] Unlike complexes **1a** or **1b**, complex **1c** afforded aldol product **6** in high yield (72 %, *syn*/*anti* 52:48) at 50 °C after only 2 h. However, **1c** did not suppress the formation of ketone **3a**, which was obtained in 28 % yield.



Scheme 2. Ru-catalyzed reaction of allylic alcohols **2** with aldehydes **4**.

We postulated that if the mechanism of the coupling occurs via Ru–enolates (Scheme 2), increasing the size of the ligands on Ru could prevent protonation at the oxygen atom and thus minimize the formation of ketone **3**. Importantly, the steric environment of the C2 carbon of the Ru–enolate, where the new C–C bond will be formed, would be affected less. We were pleased to find that the Ru complex containing a cyclopentadienyl ligand bearing five phenyl groups $[\eta^5\text{-}(Ph_5Cp)Ru(CO)_2Cl]$ (**1d**) activated by KO*t*Bu yielded aldol **5** after only 3.5 h at room temperature in >99 % yield (Scheme 2 and Table 1, entry 1) from allylic alcohol **2a** and *p*-chlorobenzaldehyde (**4a**, 1.5 equiv). Isomerization of **2a** to ketone **3a** was not detected. A variety of allylic alcohols (**2a–d**) could be coupled with a number of aldehydes (**4a–g**) affording aldols **5–14a** in excellent yields (Scheme 2, Table 1), and in most cases, under very mild reaction conditions. Furthermore, the domino transformation takes place with complete regioselectivity, as shown in entry 10, since regioisomeric aldol **14b** was not formed.[8] Unfortunately, primary allylic alcohols failed to yield the coupling product.



In an effort to understand the diastereoselectivity achieved, we followed the coupling of **2a** and **4a** in $[D_8]$toluene by ^{1}H NMR spectroscopy. We observed that at the beginning of the reaction, the *syn*-aldol was the major diastereomer (*syn*/*anti* 94:6). The ratio slowly changed as the reaction proceeded yielding higher amounts of the *anti* diastereomer (Figure 1).

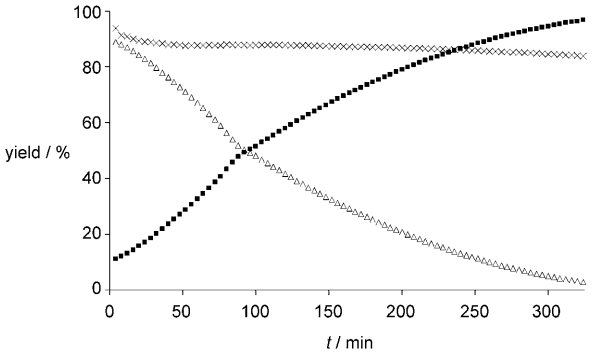
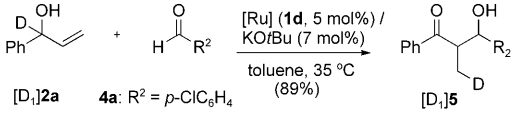


Figure 1. Cross-coupling of **2b** and **4a** in $[D_8]$toluene catalyzed by **1d** at 20 °C. $t = 0$ min corresponds to the first ^{1}H NMR spectrum recorded [Δ: **2a**; ■: **5** (*syn* + *anti*); ×: % of *syn* in **5**].

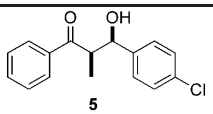
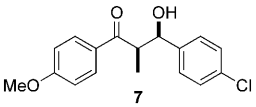
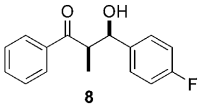
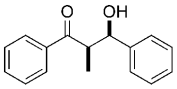
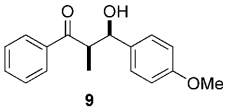
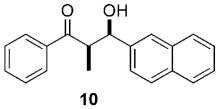
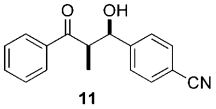
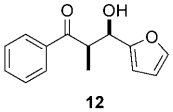
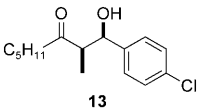
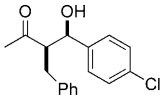
The cross-coupling between deuterated allylic alcohol $[D_1]$**2a** and aldehyde **4a** afforded monodeuterated aldol $[D_1]$**5**, with the deuterium label exclusively on the methyl group (Scheme 3).



Scheme 3. Coupling of a deuterium-labeled allylic alcohol.

Based on the results shown above, we propose the mechanism shown in Scheme 4. Ruthenium chloride **1d** reacts with KO*t*Bu forming a ruthenium *tert*-butoxide complex ($L_nRuOtBu$, **15**).[6d,e–9] Reaction of **15** with allylic alcohol **2a** gives a new alkoxide **16**,[4,7,10] as detected by ^{1}H NMR spec-

Table 1. Cross-coupling between allylic alcohols and aldehydes catalyzed by Ru complex **1d**.[a]

Entry	T [°C]/t [h]	Aldol/Ketone [%][b]	Aldol product	Yield [%][c]/*syn*:*anti*[d]
1	25/3.5	**5**/**3a** (>99:<1)	 **5**	>99 (88)/77:23
2	25/4	**7**/**3b** (>99:<1)	 **7**	>96[e]/79:21
3	25/3.5	**8**/**3a** (>99:<1)	 **8**	99 (78[f])/83:17
4	35/2.5	**6**/**3a** (99:1)	 **6**	97 (84)/69:31
5	35/1	**9**/**3a** (95:5)	 **9**	95 (93)/60:40
6	25/5	**10**/**3a** (99:1)	 **10**	97 (82)/82:18
7	50/7	**11**/**3a** (>99:<1)	 **11**	92 (80)/82:18
8	25/7	**12**/**3a** (>99:<1)	 **12**	>99 (78)/70:30
9	65/18	**13**/**3c** (>99:<1)	 **13**	69 (59)/60:40
10	35/5	**14**/**3d** (>99:<1)	 **14a**	>95 (79)/40:60 [g]

[a] See Experimental Section. [b] Determined by ^{1}H NMR spectroscopy of the crude mixture. [c] Isolated yield in parentheses. [d] Determined by ^{1}H NMR spectroscopy. [e] **7** could not be separated from traces of **2b**. [f] Only *syn*-**8** was isolated. [g] At RT, **14** was obtained in 75% yield, *syn*/*anti* 80:20 after 24 h.

troscopy (see Supporting Information). Next, β-hydride elimination forms intermediate **17** where the α,β-unsaturated ketone stays coordinated to the Ru–hydride. This is supported by the fact that the aldehyde (**4**) is not reduced to benzyl alcohol by Ru–H species. 1,4-Addition of the hydride yields Ru–enolate **18**. We believe that *cis*-enolates are produced since 2-cyclohexen-1-ol failed to isomerize to cyclohexanone or to yield any aldol in the presence of **4a** (Scheme 5). Instead, traces of 2-cyclohexenone and *p*-chlorobenzyl alcohol were detected. Thus, β-hydride elimination occurs, but subsequent 1,4-addition of the hydride to the double bond does not take place. This experiment suggests that an s-*cis* conformation of the unsaturated ketone, impossible for 2-cyclohexenone to adopt, is required for the 1,4-hydride addition to occur. Therefore, from the s-*cis* conformation of **17**, hydride addition yields a *cis*-enolate (**18**). Formation of the *syn*-aldol from *cis*-enolate-**18** and aldehyde **4** can be explained by a Zimmerman–Traxler six-membered transition state.[11] The *anti*-aldol may be mainly produced by Ru-catalyzed epimerization of the *syn*-aldol. It is known that **1d** catalyzes the fast racemization of *sec*-alcohols.[6c–d]

In conclusion, we have developed a Ru-catalyzed coupling of allylic alcohols and aldehydes under mild reaction conditions where the formation of ketones (**3**) or other by-products (benzyl alcohols or α,β-unsaturated ketones) is completely suppressed, and aldols are obtained in up to 99% yield in high *syn*/*anti* ratio.

Experimental Section

General procedure for the cross-coupling reactions: KO*t*Bu (56 μL; 0.5 M in THF, 7 mol%) was added to a mixture of complex **1d** (13 mg, 0.020 mmol, 5 mol%) and Na_2CO_3 (42 mg, 0.4 mmol) in degassed toluene (1 mL) under a nitrogen atmosphere. The mixture was stirred for 3 min before a solution of the allylic alcohol alcohol (2, 0.4 mmol) and aldehyde (**4**, 0.6 mmol) in degassed toluene (1 mL) was added via syringe. The mixture was then stirred at the appropriate temperature (see Table 1). Aliquots were taken and analyzed by ^{1}H NMR spectroscopy. When the analysis showed that no allylic alcohol (**2**) was left, the products were isolated by column chromatography (pentane/AcOEt 100:1→10:1), usually as an inseparable mixture of *syn* and *anti* diastereomers.

Acknowledgements

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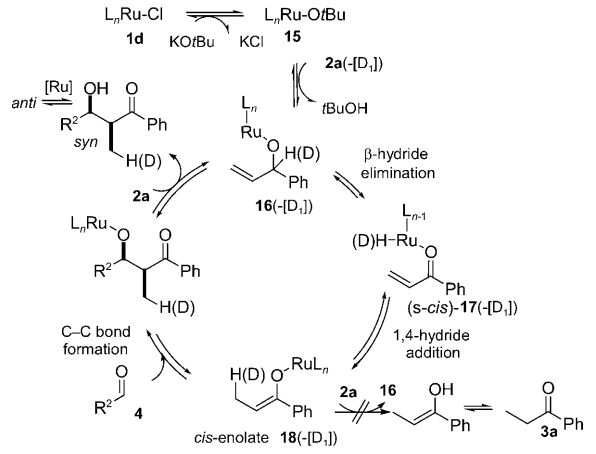
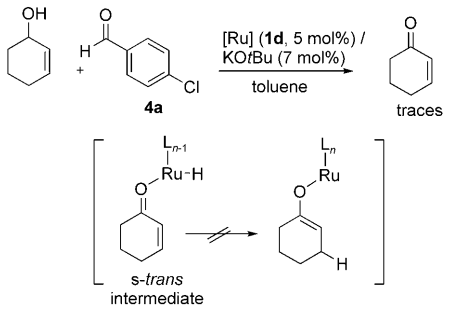


Scheme 4. Proposed catalytic cycle.



Scheme 5. Unsuccessful coupling of 2-cyclohexen-1-ol with **4a**.

Keywords: aldol reaction · allylic compounds · C–C coupling · isomerization · ruthenium

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[8] Compound **14b** could have been formed via isomerization of alcohol **2d** to the corresponding ketone (**3d**) followed by aldol reaction catalyzed by traces of base.

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