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Selective base-free transfer hydrogenation of α,β-unsaturated carbonyl compounds using *i*-PrOH or EtOH as hydrogen source

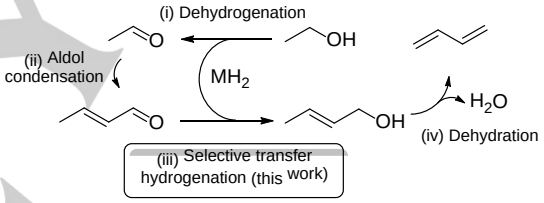
Ronald A. Farrar-Tobar,[a] Zhihong Wei, [a] Haijun Jiao, [a] Sandra Hinze, [a] Johannes G. de Vries*[a]

Abstract: Commercially available Ru-MACHO^{TM}-BH is an active catalyst for the hydrogenation of several functional groups and for the dehydrogenation of alcohols. Herein, we report on the new application of this catalyst to the base-free transfer hydrogenation of carbonyl compounds. Ru-MACHO^{TM}-BH proved to be highly active and selective in this transformation, even with α,β-unsaturated carbonyl compounds as substrates. The corresponding aliphatic, aromatic and allylic alcohols were obtained in excellent yields with catalyst loadings as low as 0.1-0.5 mol% at mild temperatures after very short. This protocol tolerates *i*-PrOH and EtOH as hydrogen sources. Additionally, scale up to multigram amounts was performed without any loss of activity or selectivity. An outer-sphere mechanism has been proposed and the computed kinetics and thermodynamics of crotonaldehyde and 1-phenyl-but-2-en-one are in perfect agreement with the experiment.

Introduction

The dwindling supply of fossil fuels[1] demands new strategies to cover our needs in terms of fuels and chemicals. For the production of chemicals, non-edible biomass is the alternative feedstock of choice. Several biomass-derived platform chemicals are already available and much research is devoted towards their conversion into existing and new bulk and fine chemicals.[2] Bioethanol, a well-known renewable platform chemical,[3] is already produced on large scale via fermentation using lignocellulose as raw material.[4] EtOH constitutes a starting material for a number of interesting compounds[5] such as butanol,[6] ethylene,[7] or 1,3-butadiene.[8] Butadiene has a huge economic value as bulk chemical with a projected worldwide production of 12.7x10^5 t/a in the year 2017.[9] It is mainly used in rubber production.

During World war II butadiene was produced from ethanol using the Lebedev and Ostromislensky processes, where the first one is a one-step process using SiO_2-MgO-Ta_2O_5 at up to 450°C, and the second one is a two-step process using (2% Ta_2O_5/ 98% SiO_2) at 350°C.[10] However, once World War II was over, and oil became readily available again, butadiene was produced from oil by cracking. The Ostromislensky process is still in use today in China, India and Russia.[11] A major drawback of this process is the low selectivity towards butadiene which never exceeded 60 %. In the last years, much research was devoted to improve the heterogeneously catalyzed process,[12] and yet, a process competitive to the production of butadiene from oil was not found. The mechanism for the synthesis of butadiene from EtOH remains unclear and is still studied intensively.[13] The most accepted mechanistic proposal includes EtOH dehydrogenation to acetaldehyde followed by aldol condensation to give crotonaldehyde, which is reduced to crotyl alcohol using ethanol as reductant. Dehydration of crotyl-alcohol delivers butadiene (Scheme 1).



Scheme 1. Most accepted mechanism for the synthesis of 1,3-butadiene from EtOH.

We envisioned an entirely new approach to increase the overall selectivity to butadiene: (*a*) to separate all steps; (*b*) to optimize each step with respect to conversion and selectivity and (*c*) to recombine all steps in a sequential flow process.
One of the key steps of the process is the third step, namely the transfer hydrogenation of crotonaldehyde to crotyl alcohol. We intend to use the starting material ethanol as reductant (Scheme 1) as the formed acetaldehyde can be used in the aldol condensation (step ii). Although the selective hydrogenation of α,β-unsaturated aldehydes is a well-researched area, much less has been published about the selective transfer hydrogenation of these substrates. [14] With heterogeneous catalysts selectivity rarely exceeds 90%. Higher selectivities can be obtained with homogeneous metal catalysts. In particular ruthenium complexes have been used. Surprisingly little is known about the use of ethanol as reductant in the transfer hydrogenation of aldehydes and ketones. So far, three examples were published reporting on homogeneous Ru, Rh and Ir complexes with sophisticated ligands, which are active with ethanol as hydrogen source (Figure 1).[15] None of these catalysts has been reported to be active for the selective reduction of α,β-unsaturated carbonyl compounds though. Reports on the selective transfer hydrogenation of α,ß-unsaturated carbonyl compounds utilize

[a] R.A. Farrar-Tobar, Z. Wei, Dr. H. Jiao, Dr. S. Hinze, Prof. Dr. J.G. de Vries
Leibniz Institut für Katalyse e. V. an der Universität Rostock
Albert-Einstein-Straße 29a, 18055 Rostock (Germany)
E-mail: johannes.devries@catalysis.de

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different kinds of hydrogen sources but not ethanol.[16] To the best of our knowledge, there is no homogeneous catalyst which is applicable for this purpose and meets the requirements for a catalyst system, namely, being cost-effective, robust and readily available.

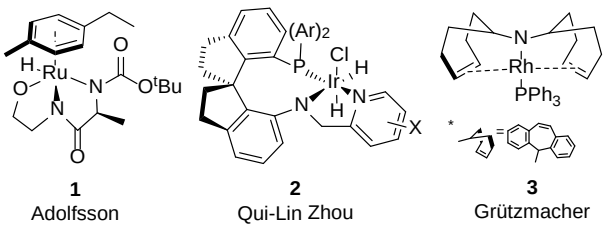


Figure 1. Active complexes reported for the transfer hydrogenation of aldehydes and ketones with ethanol as hydrogen source.

Results and Discussion

We started off with a catalyst screening (Figure 2, Table 1) for the transfer hydrogenation of crotonaldehyde (**8a**) to crotyl alcohol (**9a**). Having previously developed ruthenacycles as transfer hydrogenation catalysts we started the screening with complex **4**.[17] Also, the Shvo catalyst (**5**)[18] and its Fe analogue, Knölker's complex (**6**)[19] were candidates in view of their known activity in transfer hydrogenation. Finally, commercially available Ru-MACHO^{TM}-BH[20] (**7**) was also tried. This last catalyst is well-known for hydrogenation of challenging functional groups such as esters or nitriles,[21] for the dehydrogenation of primary and secondary alcohols,[22] and other transformations.[23]

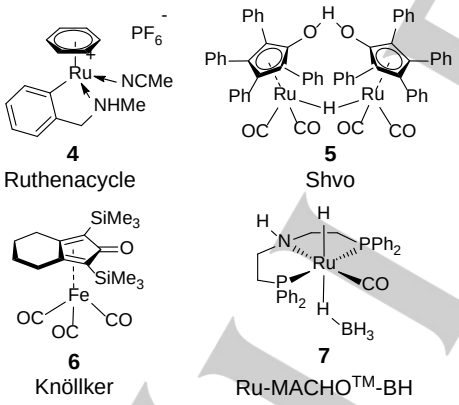
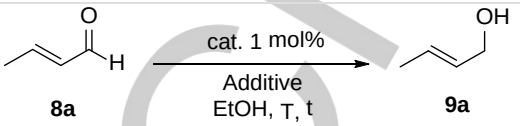


Figure 2. Selected complexes for the catalyst screening.

Catalyst **3** turned out to be very active and selective in the desired transformation (Entry 1). Nevertheless, the price of both metal and ligand in addition to the instability of the catalyst make this catalyst less suitable for our goals. The use of catalyst **4** in combination with KO*t*Bu led to full conversion of crotonaldehyde but no yield of the desired product was observed (Entry 2). This result may be due to the instability of α,β-unsaturated carbonyl compounds in basic media. Indeed, treatment of crotonaldehyde with KO*t*Bu rapidly leads to a multitude of products. Therefore, a base-free system was required. Since most modern transfer hydrogenation catalysts need activation with an excess of base, this rather reduces the number of available catalysts.[16d, 24]

Table 1. Catalyst screening for the transfer hydrogenation of crotonaldehyde.[a]



Entry	Cat.	Additive	Temp. [°C]	Conv.[b] [%]	Yield[b] [°C]
1.[c]	**3**	-	rt	>99	>99
2.	**4**	*t*-BuOK	rt	>99	0
3.	**5**	-	45	40	32
4.	**6**	$(CH_3)_3NO$	50	66	8
5.	**7**	-	refl.	>99	70
6.[d]	**7**	-	refl.	>99	97

[a] Reaction conditions: substrate(1mmol), solvent EtOH (10 ml), reaction advance monitored by T.L.C. and GC, system equipped with an exist for gases, overnight reactions. [b] Determined by GC with dodecane as internal standard. [c] Reaction time: 2 minutes. [d] *i*-PrOH used as hydrogen source and solvent

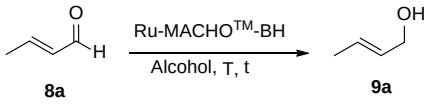
Since the Shvo catalyst (**5**) does not need base activation it is an interesting candidate. Nevertheless, conversion and yield remained low even after optimization of the temperature (Entry 3). Use of the Knölker catalyst (**6**) did not lead to better results (Entry 4). Presumably, trimethylamine formed from the additive trimethylamineoxide, which is needed for its activation, is catalysing non-desired reactions.

On the other hand, when crotyl aldehyde was dissolved in EtOH with Ru-MACHO^{TM}-BH (**7**), 70% of the desired product was formed after only 10 minutes. This result is very gratifying taking into account all the possible by-products that could form through condensation between crotyl aldehyde, crotyl alcohol, EtOH and acetaldehyde.

Next, the reaction conditions were optimized with regard to conversion and selectivity (Table 2). Using ethanol as hydrogen source at room temperature in an over-night experiment led to very low conversion (Entry 1). Raising the temperature clearly improved the yield of crotyl alcohol and allowed a drastic reduction of the reaction time to 10 minutes (Entries 2 and 3). Thus, a maximum yield of 70% was achieved at complete conversion. Similar yields were obtained using 0.1 mol% of **7** (Entry 4). At lower catalyst loadings no reaction was observed at all. Consequently, we defined the conditions in Table 2, entry 4 as standard conditions.

We also tested the tolerance of the protocol to water by running the reaction in a mixture of EtOH/H_2O (9/1). The reaction worked, but slowed down tremendously: after 3h a yield of 17% was obtained at a conversion of 47% (Entry 5).

Table 2. Optimization of reaction conditions for the Ru-MACHO^{TM}-BH (**7**) catalysed transfer hydrogenation of crotonaldehyde to crotyl alcohol.[a]

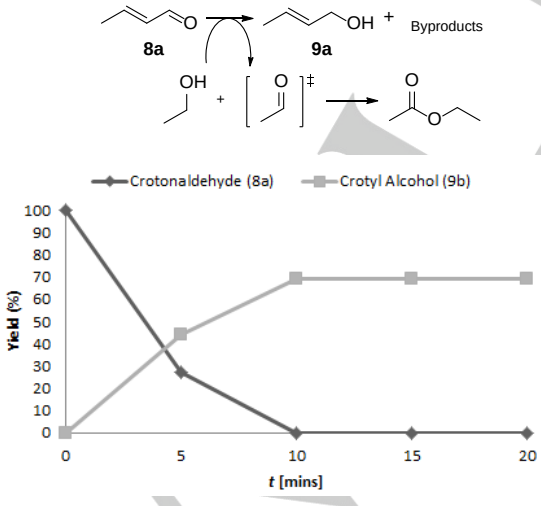


8a **9a**

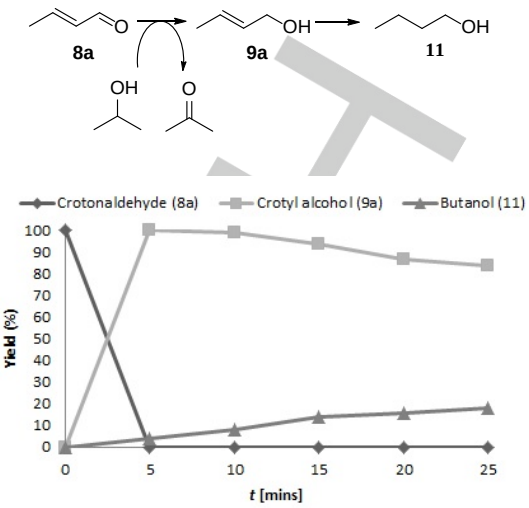
Entry	Alcohol	Temp. [°C]	Cat. [mol%]	Time [min]	Conv.[b] [%]	Yield[b] [%]
1	EtOH	rt	1	16h	12	5
2	EtOH	50	1	60	98	56
3	EtOH	refl.	1	10	>99	70
4	EtOH	refl.	0.1	10	>99	69
5	EtOH/H_2O[c]	refl.	1	60	39	14
6	*i*-PrOH	refl.	1	6.5	>99	>99
7[d]	*i*-PrOH	refl.	0.1	6.5	>99	>99 (89)[e]
8	Cyclo-hexanol	90	0.1	6.5	>99	>99

[a] Reaction conditions:4.7 mmol croton aldehyde, 20 mL alcohol. [b] Determined by GC with dodecane as internal standard. [c] Ratio: EtOH/H2O=9/1. [d] 24.3 mmol crotonaldehyde (2 mL), 80 mL solvent. [e] Isolated yield.

In addition, *i*-PrOH used as hydrogen source turned out to be more active and selective (Entries 6 and 7). In order to prove the applicability of this process, the reaction was scaled up to 2 mL of substrate, without any loss in selectivity (Entry 7). The desired product crotyl alcohol was isolated in 89% yield. Other heavier secondary alcohols, such as cyclohexanol, can also be applied successfully as hydrogen source in our protocol (Entry 8).



Scheme 2. Monitoring reaction of the transfer hydrogenation in EtOH.



Scheme 3. Monitoring reaction of the transfer hydrogenation in *i*-PrOH.

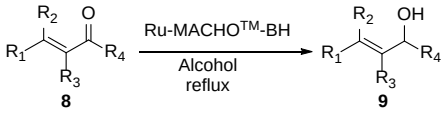
Cyclohexanone was detected in the reaction mixture as a consequence of the transfer hydrogenation. This reductant allows isolation by distillation of low boiling alcohols.

Next, the reactions in EtOH and *i*-PrOH as solvents were followed over time (Schemes 2, 3). We not only observed differences in rate and yield, but also in selectivity. When EtOH was used, ethyl acetate was detected in the reaction mixture as a major side product, which is formed upon reaction of EtOH with acetaldehyde to the hemiacetal, followed by its dehydrogenation (Scheme 2). Previous reports on transfer hydrogenation reactions with EtOH also report on ester formation.[15a, 25] We assume that some acetaldehyde also reacts with **8a** and **9a** as this accounts for the unidentified side products found in this reaction. Additional proof for the formation of acetaldehyde in this type of borrowing hydrogen chemistry can be found in the work of Krische and co-workers who reacted ethanol with dienes via its dehydrogenation to acetaldehyde.[26] When *i*-PrOH was used as hydrogen source and solvent (Scheme 3) acetone was detected as the dehydrogenation product of *i*-PrOH. In contrast to the results obtained in EtOH, the saturated alcohol is the major by-product in *i*-PrOH, which could be due to its slightly higher reflux temperature. However, this by-product is only formed after full conversion, and this allows us to stop the reaction on time to isolate the desired product in high selectivities.

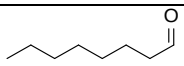
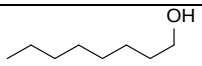
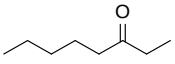
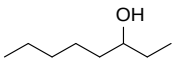
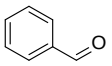
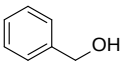
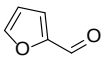
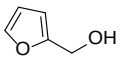
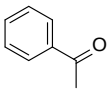
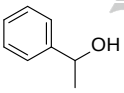
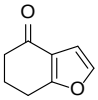
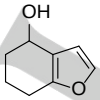
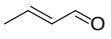
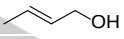
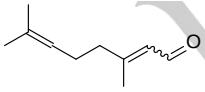
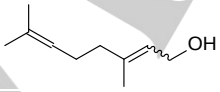
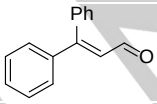
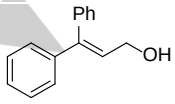
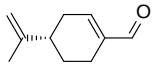
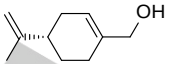
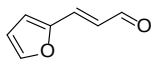
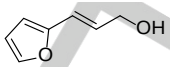
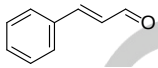
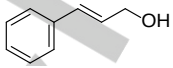
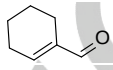
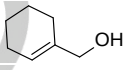
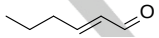
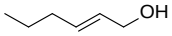
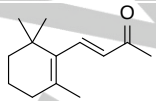
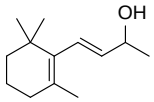
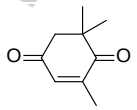
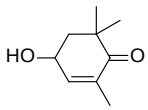
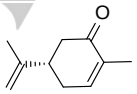
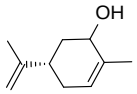
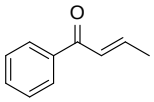
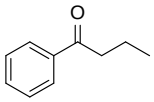
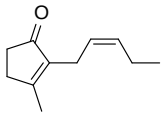
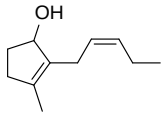
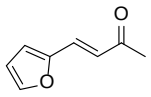
Intrigued by this new and efficient procedure for the selective reduction of crotonaldehyde, we set off to explore its scope and limitations in both solvents at reflux and 0.1 mol% catalyst loading (Table 3). Aliphatic and aromatic aldehydes and ketones were selectively reduced with very good conversions and yields (Table 3, entries 1-6). Representative examples of an aliphatic aldehyde (**8b**) and ketone (**8c**) led to the corresponding alcohol with high yields using EtOH as H_2 source (89% and 80% respectively, Table 3, entries 1-2). Also, benzaldehyde (**8d**), for was converted to benzyl alcohol (**9d**) in good yields in EtOH and *i*-PrOH (71% and 87%, respectively, Table 3, entry 1). The α,β-

unsaturated substrates are of course more challenging, as formation of the saturated side-product needs to be prevented. Gratifyingly, our protocol delivered excellent yields and selectivities towards the unsaturated primary alcohols in the transfer hydrogenation of α,β-unsaturated aldehydes (Table 3, entries 7-14, 62 to 99% isolated yields). Taking citral (**8h**) as example, we were able to show that both EtOH and *i*-PrOH can be used as hydrogen source, giving very good isolated yields (Table 3, entry 6, 97% in both cases). In addition,

Table 3. Substrate scope of the Ru-MACHO^{TM}-BH catalysed transfer hydrogenation.[a]



8 **9**

Entry	Substrate	Product	Yield [%]
1	 **8b**	 **9b**	89[b]
2	 **8c**	 **9c**	80[b]
3	 **8d**	 **9d**	87 71[b]
4	 **8e**	 **9e**	79
5	 **8f**	 **9f**	>99
6	 **8g**	 **9g**	72[e]
7	 **8a**	 **9a**	89[c]
8	 **8h**	 **9h**	97[b][e]
9	 **8i**	 **9i**	97
10	 **8j**	 **9j**	73[e]
11	 **8k**	 **9k**	>99
12	 **8l**	 **9l**	95[e]
13	 **8m**	 **9m**	94[e]
14	 **8n**	 **9n**	62
15	 **8o**	 **9o**	91[b][e]
16	 **8p**	 **9p**	84[e]
17	 **8q**	 **9q**	64[e]
18	 **8r**	 **9r**	74[d][e]
19	 **8s**	 **9s**	0 0[b]
20	 **8t**	**9t**	>99[d]
21	**8u**	**9u**	66[d][b] 35[d]

[a] Reaction Conditions: substrate (4.7 mmol), *i*-PrOH (20 mL), cat. loading 0.1% mol, reflux, reaction run until starting material was consumed (from 2 to 30 mins depending on the substrate), monitored by T.L.C. and CG using dodecane as internal standard. All yields are isolated unless mentioned otherwise. [b] Isolated yield of reaction in EtOH (20 mL). [c] Crotonaldehyde (24.1), i-PrOH (80 mL), reflux, 6.5 mins. [d] CG-yield. [e] Catalyst loading 0.5 mol%.

α,β-unsaturated ketones were also converted successfully to the corresponding α,β-unsaturated secondary alcohols (entries 15-18). In the case of β–Ionone (**8o**) EtOH again proved to be an efficient hydrogen donor allowing the isolation of β-Ionol (**9o**) in 91% yield (entry 15). Interestingly, only the sterically less hindered carbonyl group was reduced when α,β-unsaturated dione (**8p**) was subjected to the transfer hydrogenation protocol (Table 3, entry 16). This was confirmed by a multiplet at 4.5 ppm in the ^{1}H-NMR for the corresponding proton attached to carbon number 4 (See supporting information). The sterically more demanding carbonyl functionality was previously reported to be reduced in alkaline media.[27]

Additionally, it is worth mentioning that non-conjugated C-C double bonds also remained untouched under the reaction conditions of this protocol (entries 8, 10, 15, 17, 19). Unfortunately, this transfer hydrogenation protocol was not successful for the reduction of cis-Jasmone (**8s**). No conversion was observed even after increasing the catalyst loading to 1 mol%. As shown in Scheme 9 (*vide infra)*, the transfer hydrogenation of **8s** has a positive Gibbs free energy and is thus not favored thermodynamically.

In the case of 1-phenyl-but-2-en-one (**8r**), the selectivity was completely reversed (Table 3, entry 18). We obtained the saturated ketone (**9r**) as main product in 74% GC-yield, while only a minor amount of the unsaturated alcohol was detected. This is likely due to steric hindrance. We also notice that steric hindrance determined the selectivity in the transfer hydrogenation of **8p** (Table 3, entry 16) and is also the most likely explanation for the moderate yield in **8q** (Table 3, entry 17).

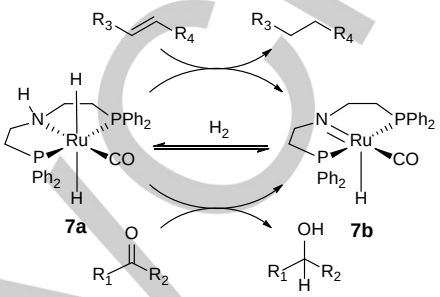
Additionally, we tested α,β-unsaturated ester (**8u**) in this transfer hydrogenation protocol (Table 3, entry 21), and obtained saturated ester (**9u**) as the main product using both EtOH and *i*-PrOH as hydrogen sources.

In summary, Ru-MACHO-BH (7) is a very efficient catalyst for the base-free transfer hydrogenation of aldehydes and ketones and very selective for α,β-unsaturated aldehydes and ketone compounds.

Mechanism of the Reaction

To understand the observed activity and selectivity, we carried out density functional theory computation on the phenyl substituted PNP amine and amido Ru catalysts (Ru-MACHO-BH, **7a** and **7b**, respectively) by using the Gaussian 09 program.[28] All structures were optimized at the B3PW91[29] level with the TZVP[30] basis set (LANL2DZ[31] for metals). All optimized structures were characterized as either energy minimums without imaginary frequencies or transition states with only one imaginary mode by frequency calculations; and the imaginary model connects the initial and the final states. The thermal correction to Gibbs free energy at 298°K from the frequency analysis was added to the total electronic energy.

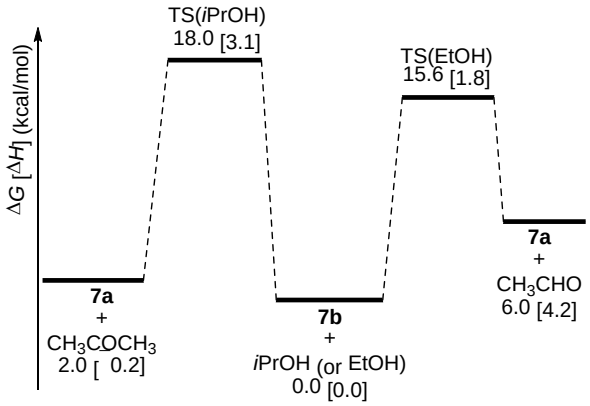
On the basis of the experimental and computed results previously reported for PNP-ligated Fe and Ru catalysts for hydrogenation reactions,[32]we propose an outer-sphere ligand to metal cooperative mechanism for the transfer hydrogenation reaction (Scheme 4). In this mechanism, it is presumed that complex **7** loses BH_3 to give complex **7a**.[21c] In contrast to previous work in which the pre-catalyst is activated by using strong base, this catalyst works well under base-free conditions. This is because BH_3 (or B_2H_6) can easily react with alcohol [B_2H_6 + ROH → H_2 + $B(OR)_3$ + $BH(OR)_2$] and thus activates the pre-catalyst **7**.



Scheme 4. Proposed hydrogenation mechanism.

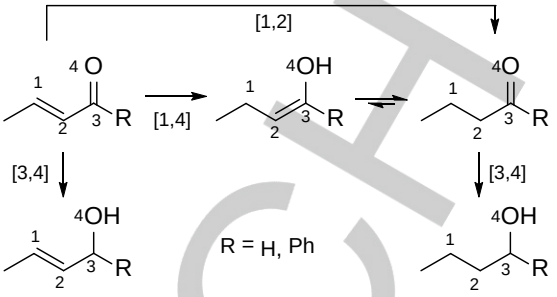
In our previous work, [21c] we found that H_2 elimination from **7a** to **7b** has a free energy barrier of 21.3 kcal/mol, and the reaction is slightly endergonic by 0.46 kcal/mol, and the barrier of the reverse H_2 addition is 20.9 kcal/mol. This reveals possible well established equilibrium and reversibility between **7a** to **7b** under H_2 atmosphere and the equilibrium state can be easily adjusted by changing H_2 pressure on the one hand; and on the other hand, it demonstrates their potential use as effective hydrogenation and dehydrogenation catalysts.

Since both EtOH and *i*-PrOH are used as H_2 source in our work, we computed their dehydrogenation on the basis of **7a** to **7b**. As shown in Scheme 5, EtOH dehydrogenation has a free energy barrier of 15.6 kcal/mol and is endergonic by 6.0 kcal/mol, while *i*-PrOH dehydrogenation has a free energy barrier of 18.0 kcal/mol and is only endergonic by 2.0 kcal/mol.

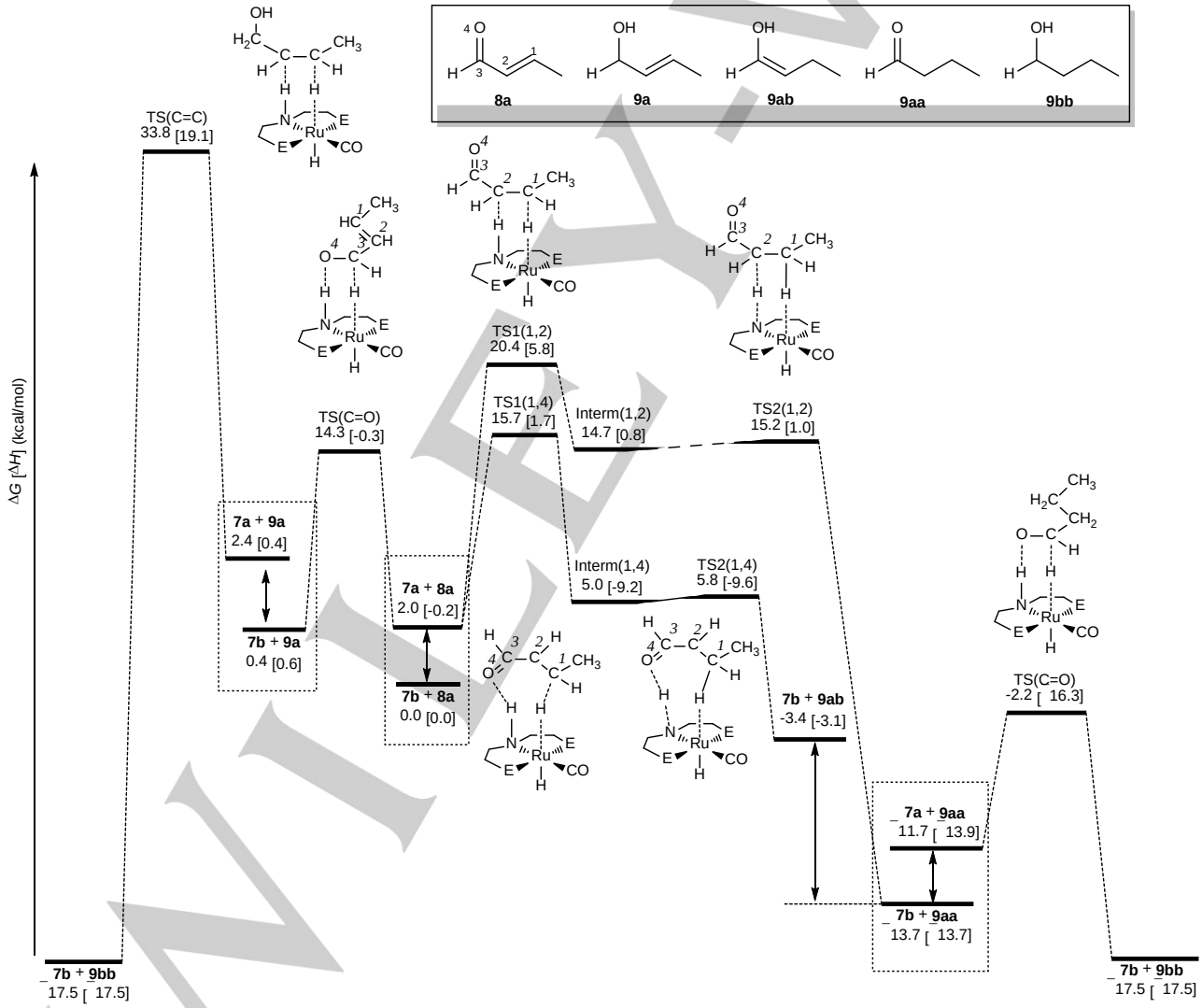


Scheme 5. Potential energy surface of EtOH and *i*-PrOH dehydrogenation using 7b as catalyst.

For our study we took (*E*)-but-2-enal (**8a**, R = H, crotonaldehyde) and (*E*)-1-phenylbut-2-en-1-one (**8r**, R = Ph) as substrates. As shown in Scheme 6, there are three competitive hydrogenation routes, the first one is the 3,4-route in which the C=O bond is hydrogenated, resulting in the formation of the allyl alcohol; the second one is the 1,2-route in which the C=C bond is hydrogenated, resulting in the formation of the saturated carbonyl compound; and the third one is the 1,4-reduction forming the enol, which can tautomerize to the saturated carbonyl compound. Therefore, both 1,2- and 1,4-routes of hydrogenation give the same product. Since the by-products of the reduction using ethanol are much more complicated than those of isopropanol due to the formation of dehydrogenative coupling of aldehydes and alcohol (ethanol and crotyl alcohol as well as crotyl addehyde and acetaldehyde), our discussion is mainly focused on the potential energy surfaces obtained by using isopropanol as hydrogen source. The computed potential energies surfaces are shown in Schemes 7 and 8.



Scheme 6. Proposed hydrogenation routes



Scheme 7. Potential energy surface of crotonaldehyde (**8a**) hydrogenation using *i*-PrOH as hydrogen source

At first we computed the selective transfer hydrogenation of (*E*)-but-2-enal (**8a**) catalyzed by **7a**. For the hydrogenation of the C=O bond (3,4-route) resulting in (*E*)-but-2-en-1-ol (**9a**) [**8a** + **7a** = **9a** + **7b**], a concerted two-bond asynchronous transition state corresponding mainly to hydride transfer is located; this step has a barrier of 12.3 kcal/mol and is exergonic by 1.6 kcal/mol. For the 1,2- and 1,4- reduction routes, we found a stepwise reaction mechanism. For the 1,2-route resulting in butyraldehyde (**9aa**) [8a + 7a = 9aa + 7b], the first step goes through the transition state for Ru-H transfer to the C1, breaking the Ru−H bond and forming the C1-H bond, resulting in an ionic intermediate; and the second step goes through the transition state of N−H transfer to the C2, breaking the N−H bond and forming the terminal C2−H bond. The free energy barrier of the Ru−H hydride transfer is 18.4 kcal/mol. The intermediate is endergonic by 12.7 kcal/mol, and the N−H proton transfer has a free energy barrier of 13.2 kcal/mol. The formation of butyraldehyde (**9aa**) is exergonic by 15.7 kcal/mol.In the 1,4-route resulting in (*E*)-but-1-en-1-ol (**9ab**) [**8a** + **7a** = **9ab** + **7b**], the first step goes via the transition state for Ru-H transfer to the C1, breaking the Ru−H bond and forming the C-H bond, resulting in an enolate intermediate. The second step goes via the transition state of breaking the N−H bond and forming the terminal O−H bond. The free energy barrier of the Ru−H transfer is 13.7 kcal/mol. The intermediate is endergonic by 3.0 kcal/mol, and the N−H proton transfer has a free energy barrier of 3.8 kcal/mol. The formation of **9ab** is exergonic by 5.4 kcal/mol. It shows that the 1,4-addition is more favored kinetically than the 1,2-addition by 4.7 kcal/mol. The tautomerization of **9ab** to **9aa** is exergonic by 10.3 kcal/mol.

In addition, we computed the subsequent hydrogenation of (*E*)-but-2-en-1-ol (**9a**) and butyraldehyde (**9aa**) to butanol (**9bb**) for comparison. For **9a** hydrogenation to **9bb**, the barrier is as high as 31.4 kcal/mol and the reaction is highly exergonic by 19.9 kcal/mol; indicating a kinetically hindered reaction. Therefore, **9a** once formed, cannot be easily further hydrogenated, despite the favored thermodynamics. For the hydrogenation of **9aa** to **9bb**, we also found a concerted two-bond asynchronous transition state corresponding mainly to hydride transfer and the barrier is 9.5 kcal/mol and the reaction is exergonic by 5.8 kcal/mol. This indicates that butyraldehyde (**9aa**), once formed, can be easily hydrogenated to butanol (**9bb** or **11**). On the basis of these competitive hydrogenation steps, one can get the selectivity between **9a** and **9aa**. As shown in Scheme 7, the barrier difference between the competitive 3,4- and 1,4-routes is only 1.4 kcal/mol, in favor of the 3,4-route.

Our results also explain the findings shown in Scheme 3 regarding isopropanol as hydrogen source. After about five minutes, **8a** is fully converted and **9a** is the major product in very high yield, while **9bb** is the minor product in very low yield. After elongated reaction time up to 25 minutes, the amount of **9a** decreases slowly, whereas the mount of **9bb** increases. Since the barrier (9.5 kcal/mol) of the hydrogenation of **9a** to **9bb** is lower than that (13.8 kcal/mol) of the reverse reaction of **9a** to **8a** and that (13.7 kcal/mol) of **8a** to **9b**, butyraldehyde (**9aa**) formation cannot be observed. This agreement validates our computational models and methods.

Since the barriers of all these favored transformation are lower than that of isopropanol dehydrogenation into acetone, the latter should be the rate-determining step. In addition, it is interesting to discuss the driving force of the formation of allyl alcohol (**9a**). On the basis of the reaction equation [**8a** + isopropanol = **9a** + acetone], this reaction is endergonic by 0.4 kcal/mol and slightly less favored thermodynamically. The driving force can be the excess of isopropanol as solvent and hydrogen source, which can shift the reaction toward formation of product **9a**. Another mechanism to drive the reaction forward might be the formed acetone, which has lower boiling point than isopropanol (56 vs. 83°C) and passes from the liquid phase into the gas phase at the boiling point of isopropanol. Such a change in physical state can also shift the reaction to product **9a**.

Furthermore, we also used cyclohexanol as hydrogen source, both cyclohexanol and cyclohexone have higher boiling points (161.8 and 155.6°C, respectively) than isopropanol and the reaction takes place at 90°C (Table 2, entry 8). Alike isopropanol as hydrogen source, the reaction with cyclohexanol as hydrogen source [**8a** + cyclohexanol = **9a** + cyclohexanone] is slightly endergonic by 1.5 kcal/mol and less favored thermodynamically. The driving force must be the excess of cyclohexanol as solvent and hydrogen source, which can shift the reaction toward the formation of product **9a**. In addition, the reaction using ethanol as hydrogen source resulting in the formation of crotyl alcohol and ethyl acetate [2×ethanol + 2×**8a** = 2×**9a** + ethyl acetate] is computed to be exergonic by 3.03 kcal/mol, a thermodynamically favoured process.

For the hydrogenation of (*E*)-1-phenylbut-2-en-1-one, only the 1,4-route of alkene hydrogenation was found (Scheme 8), all attempts to optimize the transition state of the 1,2-hydrogenation route results in the 1,4-hydrogenation route.

For the 1,4-hydrogenation route resulting in the formation of (*E*)-1-phenylbut-1-en-1-ol (**9ra**) [**8r** + **7a** = **9ra** + **7b**], the barrier for Ru-H transfer is 12.9 kcal/mol. The formation of the intermediate is endergonic by 1.9 kcal/mol, and the N-H transfer has a barrier of 2.5 kcal/mol. The formation of (*E*)-1-phenylbut-1-en-1-ol (**9ra**) is exergonic by 5.6 kcal/mol. The tautomerization of (*E*)-1-phenylbut-1-en-1-ol (**9ra**) to 1-phenylbutan-1-one (**9r**) is exergonic by 12.4 kcal/mol.

For the 3,4-route of C=O hydrogenation with the formation of (E)-1-phenylbut-2-en-1-ol (**9rb**) [**8r** + **7a** = **9rb** + **7b**], the Gibbs free energy barrier is 21.2 kcal/mol, and the reaction is endergonic by 1.1 kcal/mol.

For comparison, we computed the hydrogenation of 1-phenylbutan-1-one (**9r**) and (E)-1-phenylbut-2-en-1-ol (**9rb**) into 1-phenylbutan-1-ol (**9rc**). For the hydrogenation of **9rb** to **9rc**, a concerted two-bond asynchronous transition state corresponding mainly to hydride transfer was located, and the barrier is as high as 28.0 kcal/mol and the reaction is highly exergonic by 19.5 kcal/mol; indicating a kinetically hindered reaction. Therefore, once **9rb** formed, it cannot be easily further hydrogenated, despite the favored thermodynamics.

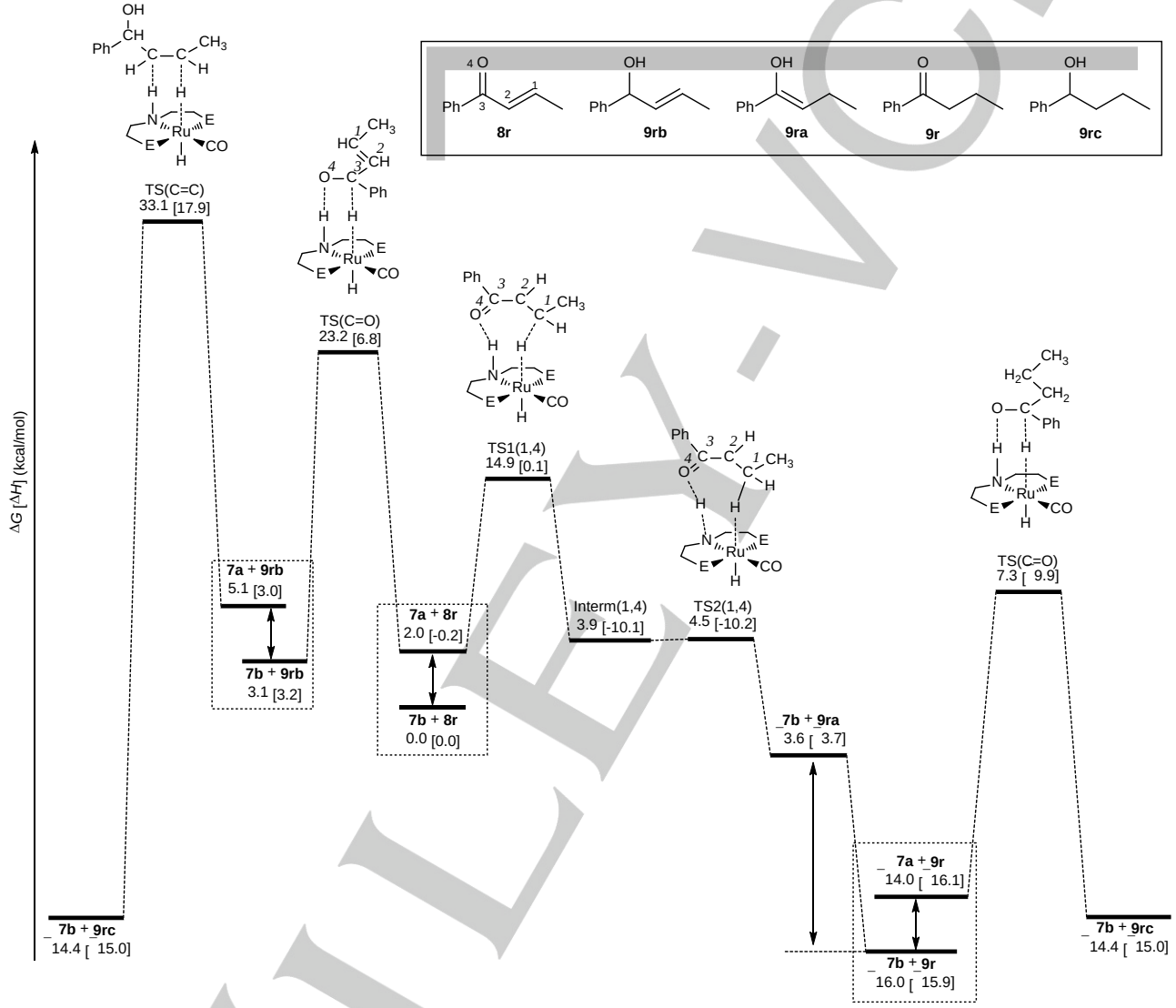
For the hydrogenation of **9r** to **9rc**, we also found a concerted two-bond asynchronous transition state corresponding mainly to hydride transfer and the barrier is 21.3 kcal/mol and the reaction is exergonic by 0.4 kcal/mol. This

indicates that once **9r** formed, it also cannot be easily hydrogenated to **9rc**. This is in good agreement with the experimental result that **9r** is the major product of the hydrogenation of **8r**.

On the potential energy surface (Scheme 7), one can see that the 1,4-hydrogenation to the enol is more favored both kinetically and thermodynamically than the C=O hydrogenation by 8.3 and 19.1 kcal/mol, respectively. This is in perfect accord with the experimental data (Table 3, Entry 18).

Since the barrier from **8r** to **9ra** is lower than that of isopropanol dehydrogenation into acetone, the latter should be the rate-determining step.

In addition, the reaction [**8r** + isopropanol = **9r** + acetone] is highly exergonic by 16.0 kcal/mol, and this should be the driving force. For using ethanol as hydrogen source, the reaction [2×ethanol + 2×**8r** = 2×**9r** + ethyl acetate] is computed to be exergonic by 35.35 kcal/mol, a thermodynamically very favoured process.



Scheme 8. Potential energy surface of (E)-1-phenylbut-2-en-1-one (8r) hydrogenation using iPrOH as hydrogen source.

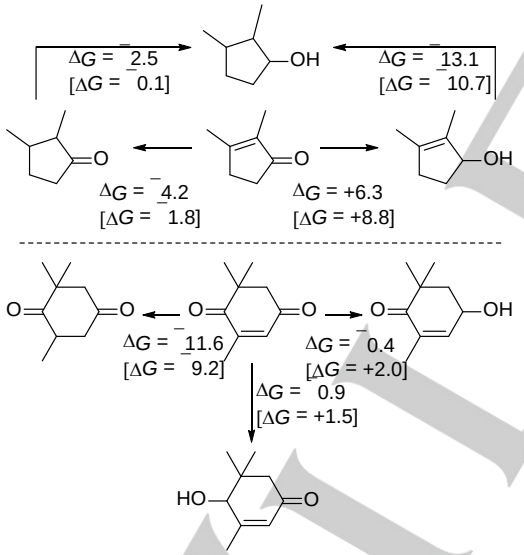
In addition, we computed the hydrogenation of 2,3-dimethylcyclopent-2-enone as a model substrate for Jasmone (**8s**, Table 3, entry 19). Basically, we computed only the thermodynamics on the basis of molecular H_2 and *i*-PrOH as hydrogen sources; and the results are listed in Scheme 9. It was found that the hydrogenation of the C=O double bond of 2,3-dimethylcyclopent-2-en-1-one is endergonic by 6.3 and 8.8 kcal/mol with molecular H_2 and *i*-PrOH as hydrogen source, respectively, indicating that this step is not favored thermodynamically. Instead, the reverse reaction, the dehydrogenation from the alcohol back to the ketone is favored thermodynamically. This endergonic property explains nicely why Jasmone (**8s**) could not be reduced in the transfer hydrogenation to the corresponding allyl alcohol.

Although the competitive C=C bond hydrogenation is favored thermodynamically with molecular H_2 as hydrogen source (ΔG =

-4.2 kcal/mol), and it becomes less exergonic (ΔG = -1.8 kcal/mol) with *i*-PrOH as hydrogen source, the barrier for this reaction on the tetra-substituted internal C=C double bond is expected to be very high for steric reasons.

Further calculations show that the hydrogenation of 2,3-dimethylcyclopent-2-enol (allyl alcohol) into 2,3-dimethylcyclopentanol is favored thermodynamically with molecular H2 and *i*-PrOH hydrogen sources (ΔG = -13.1 and -10.7 kcal/mol, respectively), but this may also not be accessible due to the high barrier caused by the sterics.

The hydrogenation of 2,3-dimethylcyclopentanone into 2,3-dimethylcyclopentanol is less exergonic with molecular H_2 and *i*-PrOH as hydrogen source (ΔG = -2.5 and -0.1 kcal/mol, respectively). Finally, we computed the thermodynamics and kinetics of the hydrogenation of 2,6,6-trimethylcyclohex-2-ene-1,4-dione (**8p**) (Scheme 9). For the reduction of the less hindered C=O double bond, the reaction is exergonic with molecular H_2 as reductant (ΔG = -0.4 kcal/mol), whereas it becomes endergonic (ΔG = 2.0 kcal/mol) with *i*-PrOH as hydrogen source. In addition, the Gibbs free energy barrier for the C=O hydrogenation is 16.9 kcal/mol, which is lower than the barrier (18.0 kcal/mol) of isopropanol dehydrogenation. This indicates that it is possible to hydrogenate the sterically less hindered C=O double bond with excess isopropanol as solvent. On the other hand, hydrogenation of the more hindered C=O double bond is more exergonic with molecular H_2 as reductant (ΔG = -0.9 kcal/mol) and less endergonic (ΔG = 1.5 kcal/mol) with *i*-PrOH. The Gibbs free energy barrier is 32.8 kcal/mol; which is nearly double of that of the less hindered C=O hydrogenation, indicating a kinetically severely hindered reaction.



Scheme 9. Computed thermodynamics (kcal/mol) of the reduction of 2,3-dimethylcyclopent-2-en-1-one and 2,6,6-trimethylcyclo-hex-2-ene-1,4-dione (**8p**) with molecular H_2 and iPrOH as hydrogen source (in square brackets)

Although the C=C double bond hydrogenation is highly favored thermodynamically with molecular H_2 and *i*-PrOH as hydrogen sources (ΔG = -11.6 and -9.2 kcal/mol, respectively), the Gibbs free energy barrier for the C=C hydrogenation is as high as 31.0 kcal/mol which indicates a kinetically hindered reaction. This is in full agreement with the experimentally result (Table 3, entry 16).

Although an inner-sphere mechanism [33a] seems very unlikely, there have been two reports on the prevalence of an inner-sphere mechanism with a ruthenium catalyst containing an NH in the ligand. One was on the hydrogenation of ketones using a ruthenium catalyst, the ligand of which contained a primary amine.[33b] The other pertained to an acceptor-less alcohol dehydrogenation using a ruthenium complex containing a secondary amine in the ligand.[33c] For this reason we decided to perform additional calculations to establish if this mechanism is reasonable in our case. In this mechanism it is presumed that the ruthenium-Macho-BH catalyst first dissociates BH_3 to form **7a**. This then reacts with the carbonyl substrate to form **7b**. In the next step **7b** reacts with the alcohol forming the ruthenium alkoxide complex in which the nitrogen is protonated. In order to regenerate **7a** from this complex, the alkoxide has to undergo β-hydride elimination. In order for this to be possible, however, a free coordination site is needed. This can only be created either by CO ligand dissociation or by dissociation of one of the phosphine ligands. The CO dissociation is however highly endergonic, e.g.; CO dissociation resulting in the singlet/triplet state of PNHP-Ru-OCH_2CH_3-CO, PNHP-Ru-O^{i}Pr-CO and PNHP-Ru-H-CO is endergonic by 48.7/54.8, 44.7/52.1 and 50.5/57.9 kcal/mol, respectively, for the Ru-ethoxide, Ru-isopropoxide as well as the **7a** complexes. The de-coordination of one of phosphine ligands is also highly endergonic by 35.2 kcal/mol. As these energy costs are much higher than the barrier for the outer-sphere hydrogenation mechanism we can safely conclude that the inner-sphere mechanism is highly unlikely.

Conclusions

For the first time, commercial Ru-MACHO^{TM}-BH was used in an efficient and straightforward base-free transfer hydrogenation using low catalyst loading and short reaction times. The system allows the reduction of aromatic and aliphatic carbonyl compounds as well as α,β-unsaturated ketones and aldehydes, such as crotonaldehyde. In the transfer hydrogenation, not only the commonly used *i*-PrOH, but also EtOH can be used as hydrogen source. On the basis of the proposed outer-sphere mechanism, B3PW91 density functional theory computations were carried out and the results are in accord with a bifunctional catalysis mechanism where allylic alcohol is formed as the kinetic product from crotonaldehyde, whereas the hydrogenation of (*E*)-1-phenylbut-2-en-1-one into butyrophenone via the formation of (*E*)-1-phenylbut-1-en-1-ol as a result of 1,4-reduction is favored both kinetically and thermodynamically. The transfer hydrogenation of 2,3-dimethylcyclopent-2-enone is thermodynamically not favored. These results are in complete accord with the experimental results.

Experimental Section

General procedure for the Ru-MACHO^{TM}-BH catalysed transfer hydrogenation.

A dry 50 ml Schlenk round-bottom flask provided with a stirring bar was purged with 3 argon-vacuum cycles and charged with a solution of 4.7 mmol substrate in 20mL of solvent. The corresponding catalyst loading was added via syringe as a stock solution in anhydrous CH_2Cl_2 (17mM).

The reaction mixture was stirred at alcohol reflux. Reaction progress was monitored with TLC and GC until starting material was fully converted (from 2 to 30 minutes depending on the substrate). After that, the reaction mixture was filtered over silica and solvents were removed. The resulting product was purified by column chromatography (SiO_2; Cyclohexene:AcOEt, 4:1) with the exception of compounds **9h** and **9a** which were distilled using a Kugelrohr and an azeotropic distillation respectively.

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Keywords: base-free • transfer-hydrogenation • EtOH • α,β-unsaturated carbonyl compounds • Ruthenium • DFT

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Layout 1:

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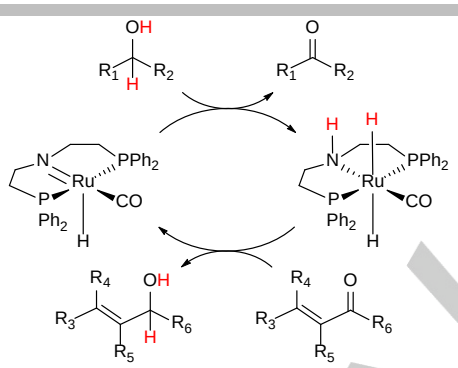
Transfer hydrogenation of α,β-unsaturated aldehydes and ketones with EtOH or *i*-PrOH can be effected using 0.1 mol% of Ru-MACHO-BH as catalyst. This catalyst does not need any base activation, thus resulting in very high selectivities.



*Ronald A. Farrar-Tobar, Zhihong Wei, Haijun Jiao, Sandra Hinze, Johannes G. de Vries**

Page No. – Page No.

Selective base-free transfer hydrogenation of α,β-unsaturated carbonyl compounds using *i*-PrOH or EtOH as hydrogen source.