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The role of acid in accelerating the asymmetric reduction of methyl acetoacetate with BINAP-chloro-(*p*-cymene)–Ru chloride complex

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Abstract

The effect of addition of organic and inorganic catalytic amounts of acid on the asymmetric hydrogenation of methyl acetoacetate with Ru–BINAP complex was studied. An increased activity was observed which was found to be dependent on the strength and the amount of acid added up to saturation. It was proposed that the added acids protonate the carbonyl bond and hence facilitate the hydride transfer.

Keywords: Methyl acetoacetate; BINAP; Asymmetric reduction

1. Introduction

The catalytic enantioselective hydrogenation of β-keto esters to the corresponding β-hydroxy esters [1] can be performed with several chiral catalysts such as Baker's yeast [1], tartaric acid modified nickel catalysts [1,2], and Ru–BINAP complexes [3–5].

Since its introduction in the beginning of the 80's by Noyori [3], the BINAP ligand has been coordinated to different transition metals [4]. The formed complexes have been acting as efficient enantioselective catalysts for various asymmetric reactions, including the reduction of carbon–carbon double bonds and carbonyl groups [3,4]. Only few papers reported on the mechanism of asymmetric reductions with Ru–BINAP [5–7]. Almost all deal with the asymmetric hydrogenation of carbon–carbon double bonds. Several Ru–BINAP complexes have been synthesized and tested already in the asymmetric reduction of methyl acetoacetate (MAA) as a representative β-keto ester [8–13]. We recently studied the role of the solvent in this reaction and found that short chain alcohols are the most efficient solvents, since they act also as proton donor and assist in the release of the product from the product-complex intermediate [14].

Several heterogeneous analogues of Ru–BINAP have also been synthesized in the past to combine the high performances of the homogeneous complexes with the ease of separation of heterogeneous catalysts [15–21]. Part of these heterogeneous catalysts were also tested in the asymmetric hydrogenation of MAA, but the activity was mostly much lower than the activity of the homogeneous parent reaction due to mass transfer limitations. Another issue of heterogenized transition metal complexes is their leaching. Due to the high solubility of Ru–BINAP in alcohols, other solvents are used preferentially to minimize complex leaching. Most often, this was also associated with decreased reaction activities.

It has been published previously that the addition of traces of strong inorganic acid to the methanolic reaction mixtures of MAA and $[RuCl_2(BINAP)_2{\cdot}NEt_3]$ enhanced activity [22]. The authors found that the reaction rate was zero order with respect to proton concentration. This effect of acid is very important for the homogeneous reaction, but even more interesting for heterogeneous Ru–BINAP analogues. Improving the catalytic performances of heterogeneous Ru–BINAP catalysts by addition of acid might increase their industrial potential.

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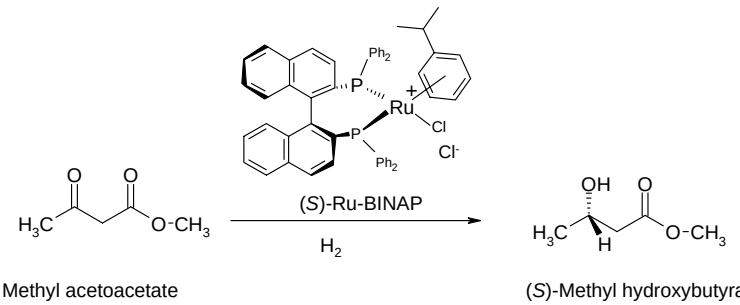

Fig. 1. Asymmetric reduction of methyl acetoacetate (MAA) to methyl hydroxybutyrate (MHB) in the presence of Ru–BINAP.

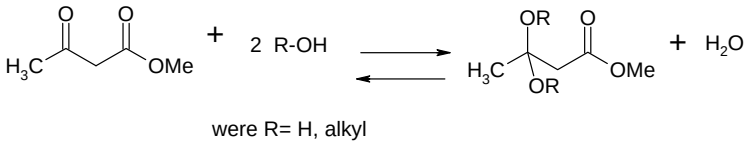

Fig. 2. Acetal formation.

2. Results and discussion

The asymmetric reduction of MAA, as a representative β-keto ester, was studied with the commercially available BINAP-chloro-(*p*-cymene)–Ru chloride complex (Fig. 1) in methanol in the presence of various organic and inorganic acids (Table 1).

As expected, the increased activities were obtained in agreement with previously published results [22]. Addition of both organic and inorganic acids to the reaction mixture increased activity up to one order of magnitude, while enantioselectivity remained almost unchanged except in the case of HCl (entry 5) and acetic acid (entry 7). Since HCl was added in aqueous solution, the small decrease in enantioselectivity in the presence of this acid might be attributed to the presence of water, proven elsewhere to decrease reaction enantioselectivity due to dissociation of the chloro ligand from the complex [14]. With acetic acid, it might be that the decreased enantioselectivity is due to competitive coordination of the acetate anion to the complex.

Since the reactions were all performed in methanol, acetal formation, favored in the presence of strong acids (Fig. 2), decreased the product selectivity (entries 2–6).

The activity of the chiral catalyst in the presence of strong inorganic acids was hardly influenced by the amount added [22]. On contrary, increasing the amount of organic acid linearly increased the activity up to a certain saturation level (Fig. 3). Increasing the strength of both organic and inorganic acids and thus decreasing their pK_a resulted in a linear increase in activity (Fig. 4). It should be taken into account that the literature pK_a values are at 25 °C for aqueous solutions [23] and the behavior of the acids in methanol is most likely different. In addition, the strength for tartaric and oxalic acids relates only to the dissociation of the first proton.

The catalytic cycle of the asymmetric reduction of MAA with Ru–BINAP complexes in methanol has been previously discussed in literature [2,24]. This cycle was adapted to the type of complex studied here (Fig. 5) and a tentative explanation is given for the effect of the added acid on the catalytic cycle. The first necessary step in the catalytic cycle is the removal of the *p*-cymene ligand from the catalyst precursor to yield three empty coordination sites (step 1), which can be captured by the solvent. One ligand position is then captured by a hydride, generated by a heterolytic dissociation of a hydrogen molecule (step 2). The substrate is then directed by the BINAP ligand via its two carbonyl groups to two coordination sites (step 3). This coordination determines

Table 1
The effect of the type and strength (pK_a) of acids and bases on the performance of Ru–BINAP in the asymmetric hydrogenation of MAA[a]

Entry	Acid	pK_a	Turn over frequency (h^{-1})	% e.e.	% Selectivity[b]
1	–	–	135.3	99	89
2	H_2SO_4[c]	–	823.2	99	73
3	H_2SO_4	–	860.4	99	73
4	H_2SO_4[d]	–	873.1	99	74
5	HCl	–	977.7	91	78
6	PTSA[e]	–	780.4	99	82
7	Acetic	4.75	165.2	87	100
8	Benzoic	4.17	185.3	97	99
9	Tartaric	2.38	216.6	97	98
10	Oxalic	1.29	344.0	99	98
11	NaOH	–	0	0	0
12	$NaCO_3$	–	0	0	0
13	PTSA[e,f]	–	758.3	99	85

[a] Reaction conditions: 60 °C, 40 atm H_2, 18 ml methanol, 2 g MAA, $S/C = 3200$, 16 μmol acid.
[b] The percentage of *R* and *S*-MHB from the converted substrate with the corresponding acetal as other product.
[c] 4 μmol acid.
[d] 32 μmol acid.
[e] *para*-Toluene sulfonic acid.
[f] 40 atm deuterium, 18 ml deuterated methanol (CD_3OD).

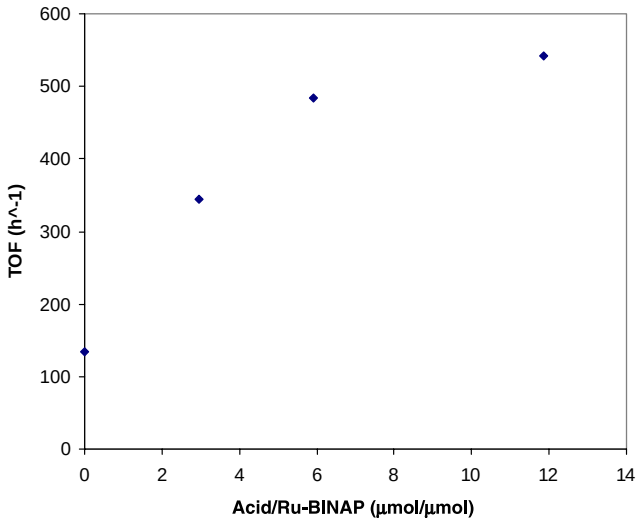

Fig. 3. Efficiency of reaction as a function of amount of oxalic acid added (the zero point activity in Fig. 3 was taken from the acid free reaction).

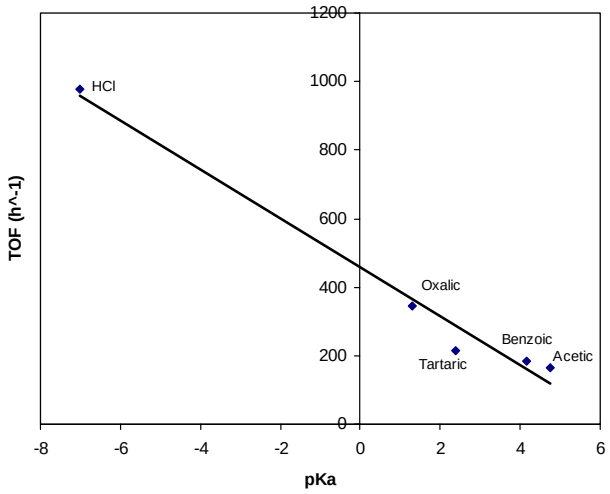

Fig. 4. The effect of the pK_a [23] of the acid on the activity of the reaction.

the enantioselectivity, since it is only possible in the specific configuration dictated by the BINAP ligand [2]. Hydride insertion to form the active product-complex intermediate follows (step 4). Finally, the chiral product is released by the attack of a proton, generated from the heterolytic dissociation of a hydrogen molecule, and hydride insertion into the complex (step 5). Alternatively, a proton can be donated by methanol (step 6), followed by a hydride insertion into the complex and the release of a methoxide group (step 7).

The enhanced activity of the chiral catalyst in the asymmetric reduction of MAA by the addition of acid could be a result of acid participation in various stages of the catalytic cycle. Better removal of the *p*-cymene ligand from the complex could be one possible route to enhance the activity by acid. However, the amount of free *p*-cymene which was detected by GC analysis in acidic conditions was unchanged. Furthermore, literature date showed that the addition of acid to Ru–BINAP complexes carrying no *p*-cymene ligand at all also resulted in an enhanced activity [22].

The increased activity in the presence of acid could be explained also by the involvement of the acid in the hydride insertion (step 4). Protonation of the substrate by the acid prior to hydride insertion could accelerate the hydride insertion (Fig. 6). Moreover, tautomerization of the substrate by addition of acid or base is also feasible (Fig. 7) [23,25]. Addition of acid could increase the reaction rate by this type of mechanism, but it implies also that the same effect would occur in the presence of base. However in the presence of bases (Table 2, entries 11, 12) no hydrogenation was obtained.

We recently reported the role of the solvent in the asymmetric reduction of MAA with Ru–BINAP [14]. It was found that short alcohols act as proton donors (Fig. 5, step 6), while the protonation of the product is by molecular hydrogen in non-protic solvents or in large and branched, thus poorly coordinating, alcohols (Fig. 5, step 5). If the acid protonates the carbonyl group and thus enhances activity, then the effect of addition of acid on activity should be higher in poorly coordinating solvents or more aprotic solvents than in methanol. Since the solubility of acids in aprotic solvent is

Table 2
Effect of acid addition on activity in alcohols in the asymmetric hydrogenation of MAA with Ru–BINAP[a]

Entry	Solvent	Acid	% Conversion	% Selectivity[b]	% Yield[c]	Relative rates[d]
1	Methanol	–	38.5	85	32.3	–
2	Methanol	PTSA	75.2	91	69.9	2.16
3	Ethanol	–	36.4	90	32.7	–
4	Ethanol	PTSA	83.0	93	77.2	2.36
5	2-Methyl-1-propanol	–	2.9[e]	100	1.9	–
6	2-Methyl-1-propanol	PTSA	20.6[e]	100	20.6	7.1

[a] Reaction conditions: 60 °C, 4 ml solvent, 0.002 g Ru–BINAP, $S/C = 130$, 0.5 h and 1 mmol *para*-toluene sulfonic acid for entries 2, 4, 6.
[b] The percentage of *R* and *S*-MHB from the converted substrate with the corresponding acetal as other product.
[c] Yield = conversion × selectivity.
[d] Relative rates: yield in presence of acid/yield in absence of acid.
[e] 1 h.

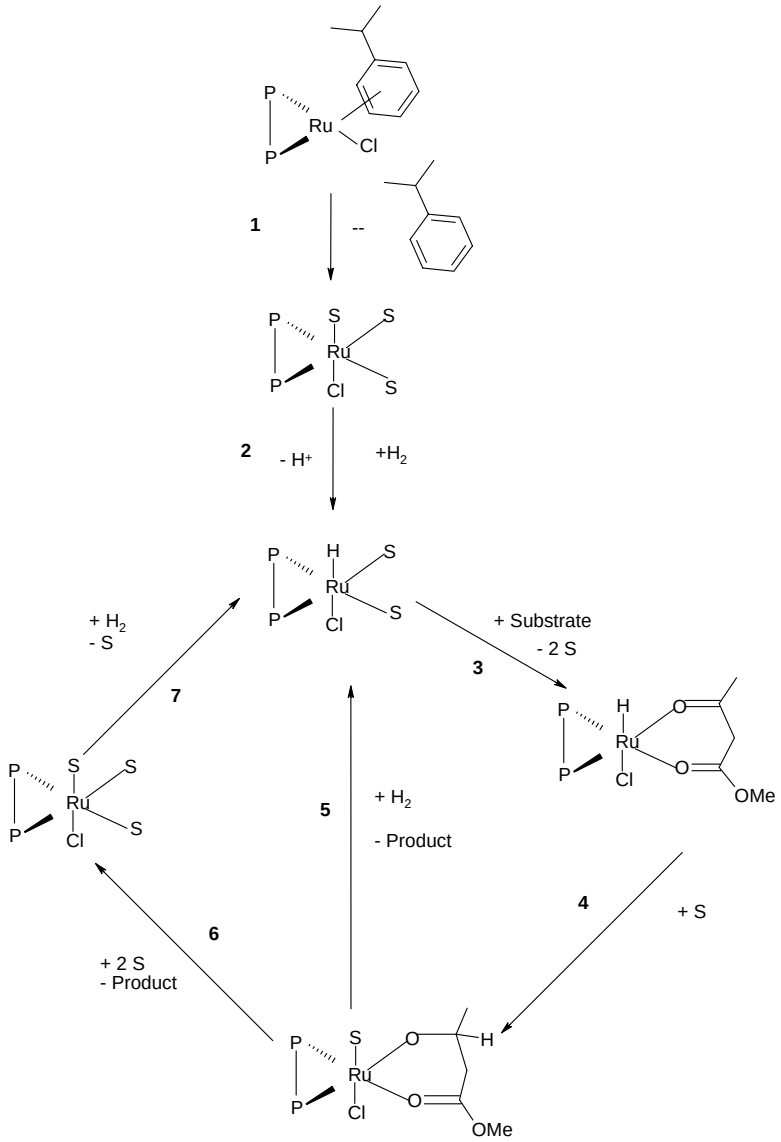

Fig. 5. The catalytic cycle for the enantioselective hydrogenation of MAA.

almost zero, we tested the effect of addition of acid on reaction in various alcohols (Table 2). While the effect of added acid on activity was almost the same in methanol (entries 1, 2) as in ethanol (entries 3, 4), it was much more significant in 2-methyl-1-propanol (entries 4, 5). This finding supports our assumption that the acid protonates the carbonyl group and hence takes over the role of the solvent under acid-free conditions. But since the solvent is also essential in the hydride insertion step (step 4), the activity in branched alcohols is still lower than in methanol, even with addition of acid.

Finally, to elucidate the origin of the proton in the final product, a reaction in fully deuterated methanol (CD_3OD) under deuterium pressure was performed in the presence of *p*-toluene sulfonic acid (PTSA) (Table 1, entry 13). GC-MS analysis of the product after the hydrogenation of MAA confirmed the presence of only one proton in the final product, obviously originating from the acid. These results suggest an alternative new catalytic cycle for the asymmetric hydrogenation of MAA in the presence of acid (Fig. 8). Although, as previously explained, MAA can form an enol in methanolic solution with added acid (Fig. 8), the protonation

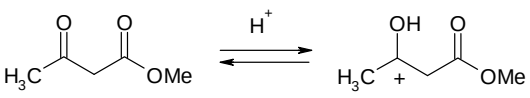

Fig. 6. Protonation of MAA with acid.

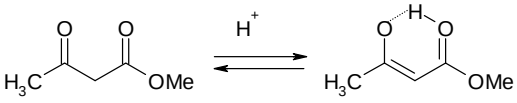

Fig. 7. Tautomerization of MAA in the presence of acid.

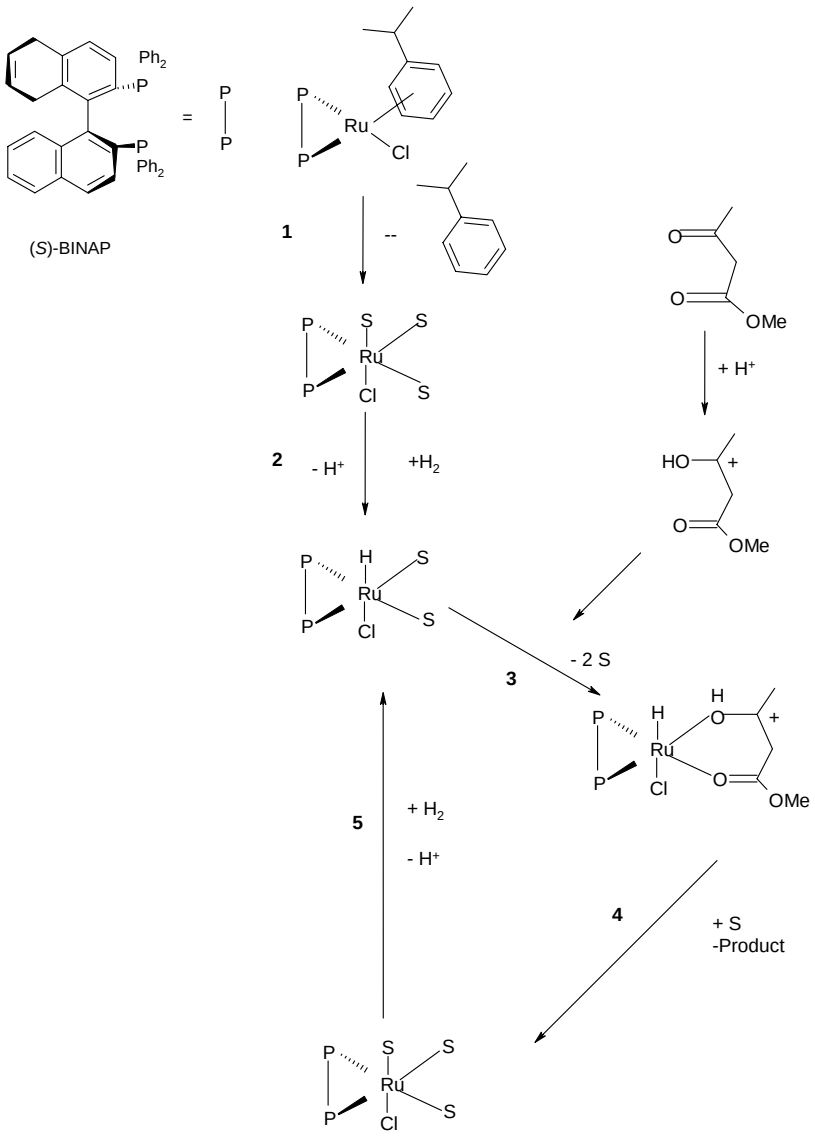

Fig. 8. The catalytic cycle in the presence of acid.

of MAA is also possible after coordination to the complex. Though acid does not dissolve in an aprotic solvent, the generation of acid sites in situ in heterogeneous Ru–BINAP analogous, for instance when using acidic zeolites as supports [26], might allow enhanced reaction in aprotic solvents.

3. Conclusions

Addition of organic and inorganic acids to the enantioselective hydrogenation of MAA in alcoholic solvents with Ru–BINAP enhanced the reaction activity up to one order of magnitude. The enhancement of activity was found to increase with increasing the strength or the amount of acid up to saturation. The mechanism of activity enhancement by acid is probably via protonation of the carbonyl group of the substrate to facilitate hydride insertion.

4. Experimental

A stainless steel reactor with magnetic stirring was used for all homogeneous reactions. The complex was first dissolved in 4–18 ml of the reaction solvent, after which 0.1–0.5 g of substrate and catalytic amounts of acid were added. Reaction was carried out at 60 °C and at a pressure of 40–60 bar hydrogen. The reactor was heated electrically and the temperature controlled with a Eurotherm. The reactor was first flushed with nitrogen followed by hydrogen flushing before stirring was started. Samples were withdrawn to determine the reaction rate and enantioselectivity.

The reaction mixture was analyzed by GC on a Chiraldex G-TA column. Turn over frequency (TOF) was calculated as moles of reacted substrate divided by moles of catalysts and reaction time in hours.

For the hydrogenation reactions with deuterium, deuterium gas replaced the hydrogen gas and CD_3OD replaced methanol. For the GC-MS analysis, a Fisons MD-800 instrument with CP-Sil 5 CB column was used.

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