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Journal of Molecular Catalysis A: Chemical 198 (2003) 39–45

JOURNAL OF MOLECULAR CATALYSIS A: CHEMICAL

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# The role of the solvent in the asymmetric hydrogenation of β-keto esters with Ru-BINAP

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Received 25 October 2002; received in revised form 25 October 2002; accepted 4 December 2002

**Abstract**

The influence of the solvent on the asymmetric hydrogenation of methyl acetoacetate, as a representative β-keto esters, with Ru-BINAP was studied. The highest activities were measured when the reaction proceeded in methanol, ethanol or isopropanol. These solvents, which also act as proton donors, accelerate product release from the reaction intermediate. The presence of water in the reaction mixture has been found to be detrimental for both activity and enantioselectivity. All results could be explained by the existence of two different solvent dependent reaction pathways for product release.


*Keywords:* Asymmetric hydrogenation; Ru-BINAP; Transition metal complex; Keto esters; Solvent effect

## 1. Introduction

The physico-chemical nature of the solvent is very important in any process that involves mass, heat or momentum transfer [1]. Of course, economic, environmental and safety requirements should also be considered in the selection of a reaction solvent. The chemical composition of the solvent can also affect activity and selectivity, and its physical properties might dictate the reaction conditions [2]. Therefore, the choice of the solvent in homogeneous and heterogeneous catalytic reactions with transition metal complexes (TMCs) has an important impact on the catalytic performance. The solubility of the reactants (gases, liquids and solids) in the reaction solvent is clearly of significant concern. While TMCs in homogeneous reactions need a good solvent to get dissolved, the use of such good solvents with entrapped catalysts might cause TMC leaching [3,4]. Changing the solvent might also alter the mass transfer of substrates and products in the heterogeneous system, and thus also the reactivity. For instance, when polymers are used to support the TMC, their degree of swelling in a certain solvent can determine the reaction rate [4,5]. In certain catalytic reactions with TMCs, the solvent also acts as a temporary ligand in the catalytic cycle [6] or as a proton donor [6,7]. Finally, it is well known that solvent impurities, even when present in trace amounts only, can deactivate metal complexes or drastically decrease their selectivity.

Many chiral ligands in combination with transition metals operate as very active and enantioselective catalysts in a variety of asymmetric reactions [3–7]. One of

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doi:10.1016/S1381-1169(02)00681-7

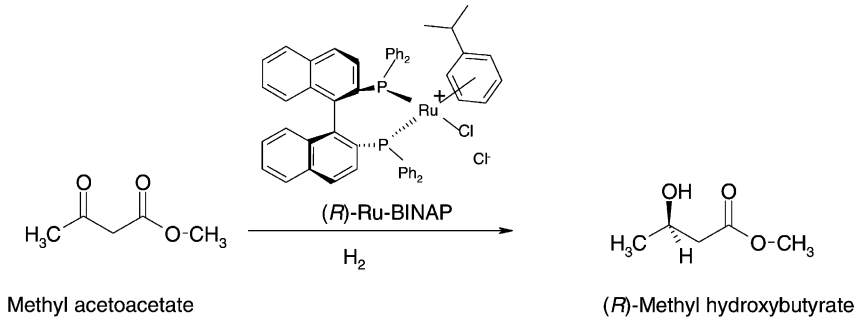


Fig. 1. The asymmetric reduction of MAA with Ru-BINAP complex.

the most versatile, and consequently most investigated, ligands is (±)-2,2′-bis(diphenylphosphino)-1,1′-binaphthalene (BINAP) ligand. It can be coupled to many transition metals, and it catalyzes a wide range of asymmetric reactions [8]. The Ru-complexes of BINAP are capable of reducing a much wider range of carbon–carbon double bonds than their Rh-counterparts. Furthermore, they are very effective catalysts in hydrogenation reactions of functionalized ketones [6,8]. While the mechanism of Rh-catalyzed asymmetric hydrogenations is rather well understood [9], only few mechanistic papers deal with Ru-BINAP complexes. Most of them concern the asymmetric hydrogenation of carbon–carbon double bonds [10–12].

Optically active β-hydroxy carboxylic acids (esters) have various applications in the synthesis of enantiomerically pure pharmaceuticals, pesticides, flavors, and as monomers for biodegradable polymers [13]. The enantioselective reduction of β-keto esters to β-hydroxy esters was successfully achieved with several types of Ru-BINAP complexes in mild conditions [14–19]. The homogeneous reaction always proceeded in methanol, ethanol or dichloromethane and the authors mainly focused on showing the scope of the new catalysts. A catalytic cycle for the asymmetric hydrogenation of β-keto esters in methanol has been suggested by Noyori, based on reaction with the achiral $RuCl_2[P(C_6H_5)_3]_3$ complex [6]. The same mechanism has been suggested lately for Ru-BINAP, however without any proof [20].

Some heterogeneous analogues of Ru-BINAP have also been prepared. Both a polymer anchored Ru-BINAP [21–25] and a polydimethylsiloxane [26] occluded catalyst were tested in the asymmetric reduction of β-keto esters. Biphasic ionic liquid systems are alternative successfully heterogenization method [27]. The role of the solvent was never explained in more detail than the link to leaching, despite the huge differences in activity observed when the solvent was changed.

Apparently, the solvent thus plays a determining role in the enantioselective reduction of β-keto esters under both homogeneous and heterogeneous conditions. This role will be illustrated in this paper and the results point to a solvent dependent mechanistic cycle for the reaction of methyl acetoacetate (MAA), as a representative β-keto esters, with the commercial BINAP-chloro-(*p*-cymene)-Ru chloride complex (Fig. 1).

## 2. Results and discussion

For most homogeneous chiral hydrogenation reactions, alcohols are the solvents of first choice since they dissolve many complexes and organic substrates easily. The enantioselective hydrogenation of MAA with Ru-BINAP proceeded with high activity and enantioselectivity in most alcoholic solvents (Table 1, entries 1–5). Some acetal formation from the reaction between the substrate and the alcohol was also observed (Fig. 2).

The reaction, without any acetal formation, can also proceed in chlorinated solvents with comparable enantioselectivity, but with lower activity (entries 6 and 7) and in acetonitrile (entry 8). However, performing the reaction in other common aprotic solvents resulted in no activity at all (entries 9–12), although both complex and substrate dissolved very well. Even in neat MAA (entry 10), in which the complex dissolved, activity

Table 1
Effect of solvent on the performance of Ru-(*R*)-BINAP in the asymmetric hydrogenation of MAA[a]

| Entry | Solvent | TOF ($h^{-1}$) | ee[b] (%) | Selectivity[c] (%) |
|---|---|---|---|---|
| 1 | Methanol[d] | 135.3 | 99 | 89 |
| 2 | Ethanol | 128.2 | 99 | 93 |
| 3 | Isopropanol | 95.1 | 99 | 93 |
| 4 | 2-Methyl-1-propanol | 8.4[g] | 99 | 100 |
| 5 | *t*-Butyl alchol | 8.1[g] | 99 | 100 |
| 6 | Dichloromethane[e] | 20.3 | 99 | 100 |
| 7 | Chloroform | 32.9 | 99 | 100 |
| 8 | Acetonitrile | 12 | 92 | 100 |
| 9 | Ethyl acetate | 0 | 0 | 0 |
| 10 | Methyl acetoacetate | 0 | 0 | 0 |
| 11 | Tetrahydrofuran | 0 | 0 | 0 |
| 12 | Methyl *t*-butyl ether | 0 | 0 | 0 |
| 13 | Xylene[f] | 1.5[g] | 5 | 100 |
| 14 | Heptane[f] | 1.7[g] | 20 | 100 |
| 15 | Water[f] | 2.5[g] | 7 | 100 |

[a] Reaction conditions: 60 °C, 40 atm $H_2$, 18 ml solvent, 2 g MAA, S/C = 3200, 1 h.
[b] (*R*)-Methyl hydroxybutyrate ((*R*)-MHB).
[c] Selectivity to MHB due to formation of the corresponding acetal.
[d] Reaction with Ru-(*S*)-BINAP yielded (*S*)-MHB.
[e] Addition of 5% (v/v) of water to dichloromethane.
[f] Dissolution of the complex in 0.5 ml methanol.
[g] 5 h.

was absent. This result could probably be explained by the difference in polarity of the aprotic solvents. Solvent polarity is a commonly used term related to the capacity of a solvent to solvate dissolved charged or dipolar species [28]. However, this concept of solvent polarity is difficult to define precisely and even more difficult to express quantitatively. Although the dielectric constant is often used to describe solvent polarity, this approach does not take into account specific solute/solvent interactions. There are several empirical parameters of solvent polarity calculated from Gibbs energy, equilibrium, kinetic and spectroscopic measurements [28], all of them pointing to the fact that the polarity of dichloromethane, chloroform and acetonitrile is higher than that of ethers and ethyl acetate. From the results in Table 1, it seems that the asymmetric reduction of MAA with Ru-BINAP is preferably performed in more polar aprotic solvents. When the complex was dissolved separately in small amounts of methanol and then added to solvents in which the complex did not dissolve, like water and hexane, very poor performances were observed, probably due to the presence of methanol traces (entries 13–15).

Since the nature of the solvent clearly affects the reaction performance due to participation in the catalytic cycle [6,21], the role of the solvent in the catalytic cycle was further investigated. The reaction cycle was adapted from literature and applied to the asymmetric hydrogenation of MAA in methanol with Ru-BINAP (Fig. 3). The first necessary step is the removal of the *p*-cymene ligand from the catalyst precursor yielding three free coordination sites (step 1) which can be captured by the solvent. One ligand position is then captured by a hydride that is generated by the heterolytic dissociation of a hydrogen molecule (step 2). The substrate then coordinates via its two carbonyl groups to the two remaining coordination sites (step 3). It is this coordination that is only possible in the configuration dictated by the BINAP ligand [6], and hence determines the enantioselectivity. After hydride insertion, the active intermediate is formed (step 4), and the chiral product can be released by a proton attack via two different pathways. A proton, generated from the heterolytic dissociation of a hydrogen molecule on the metal complex, can attack the carbonyl oxygen while the hydride captures the free coordination site (step 5). Alternatively, a proton is transmitted from protic solvent (step 6), followed by the release of an alkoxide group and generation of a new active species by gaseous hydrogen (step 7).

According to this proposed catalytic cycle, the solvent thus has a role in two different catalytic steps. It assists in the hydride insertion from the complex to

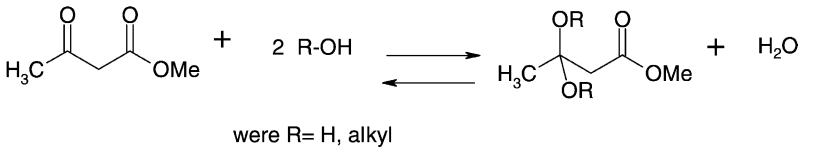


Fig. 2. Formation of acetal of MAA in alcoholic solvents.

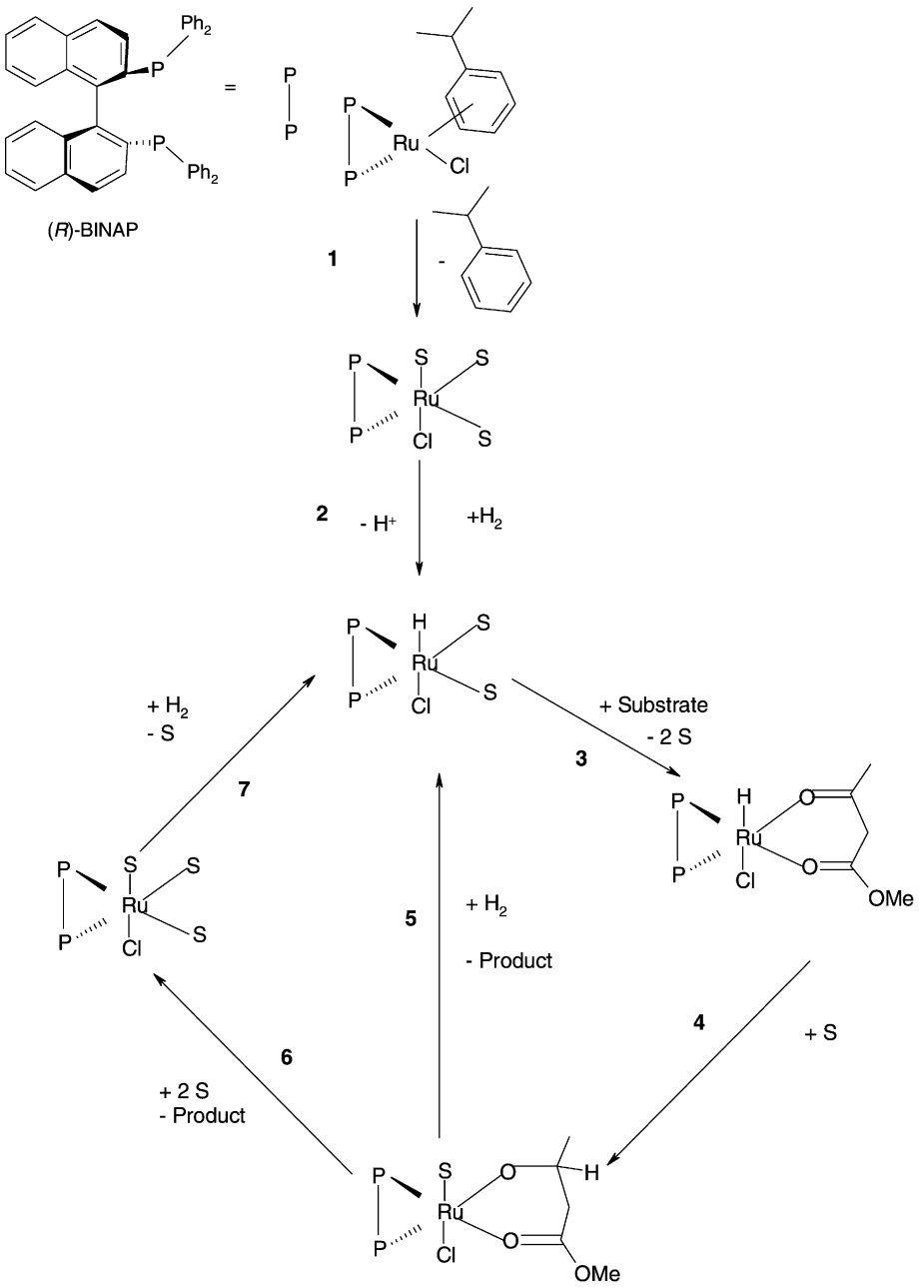


Fig. 3. Proposed catalytic cycle for the enantioselective hydrogenation of MAA.

the substrate by replacement of the hydride (step 4), and it helps in releasing the product from the complex by proton transfer from the solvent (step 6). While protic solvents, like alcohols, can donate their proton, aprotic solvents can not. Therefore, the protonation of the product in aprotic solvents must come from gaseous hydrogen (step 5) with the elimination of steps 6 and 7. It is reasonable to assume that,

like in the asymmetric reduction of α,β-unsaturated carboxylic acids with Ru-BINAP dicarboxylate complexes of the type Ru(II)$(OOCR)_2$(BINAP), the protonation of the product by proton transfer is much faster than its protonation by gaseous hydrogen [10,11]. This assumption can explain the higher reactivity of MAA in the alcohols used (Table 1, entries 1–4) than in aprotic solvents (Table 1, entries 6–12). Indeed, when hydrogenations of MAA with Ru-BINAP were performed in methanol with deuterium or in deuterated methanol with molecular hydrogen, GC/MS analysis of both reactions mixture revealed the presence of both deuterated and non-deuterated methyl hydroxybutyrate. When the reaction was performed in $CDCl_3$ with molecular hydrogen, no deuterated product was observed.

For alcoholic solvents, going from methanol to *t*-butyl alcohol resulted in lower activity, higher chemoselectivity and unchanged enantioselectivity (Table 1, entries 1–5). This different reactivity could be linked to the p$K_a$ of the linear alcohols regarding the dissociation of the proton from the alcohol, which leads to a reduced protonation of the product and hence lowered activity. Methanol and ethanol have the same p$K_a$ of 16 [29] leading to similar yields (Table 1, entries 1 and 2), while the p$K_a$ of isopropanol is slightly higher (17) [30], leading to lower yields (Table 1, entry 3). It is clear from Table 1 (entries 4 and 5) that the bad coordination of larger branched alcohols leads to a severe drop in activity. Indeed, although the p$K_a$ of isopropanol and *t*-butyl alcohol are almost equal, the activity in *t*-butyl alcohol is much lower.

To further support the proposed catalytic cycle, the effect of hydrogen pressure on the asymmetric reduction of MAA was tested in both methanol and dichloromethane (Table 2). Assuming a first order dependence on hydrogen pressure [11] in step 5, it was anticipated that an increased hydrogen pressure in dichloromethane would increase activity, due to an enhanced protonation of the product by gaseous hydrogen (step 5). The same can of course also happen for the reaction in methanol, but the increased gas pressure could also increase the rate of protonation of the methoxide and its release from the complex (step 7). The effect of increasing hydrogen pressure on the methanol reaction might thus be stronger. The results in Table 2 indeed confirmed the suppositions. In dichloromethane, the TOF increased 1.5 times with a similar increase in pressure, while the enantioselectivity decreased slightly. In methanol on the other hand, the activity did not follow a first order dependency on hydrogen pressure, but the TOF increased by a factor of 2.1, with a decrease in enantioselectivity.

Table 2
Effect of hydrogen pressure on the performance of Ru-(*R*)-BINAP in the asymmetric hydrogenation of MAA in methanol and dichloromethane[a]

| Entry | Solvent | Pressure (bar) | TOF ($h^{-1}$) | ee[b] (%) | Selectivity[c] (%) |
|---|---|---|---|---|---|
| 1 | Dichloromethane | 40 | 28.4 | 99 | 100 |
| 2 | Dichloromethane | 60 | 42.1 | 93 | 100 |
| 3 | Methanol | 40 | 102 | 99 | 85 |
| 4 | Methanol | 60 | 213 | 89 | 85 |

[a] Reaction conditions: 60 °C, 4 ml solvent, 0.002 g Ru-BINAP, S/C = 130, 0.5 h.
[b] (*R*)-Methyl hydroxybutyrate ((*R*)-MHB).
[c] Selectivity to MHB due to formation of the corresponding acetal.

The results in Tables 1 and 2 and GC/MS results prove the existence of two different solvent dependent pathways to release the product in the asymmetric reduction of MAA with Ru-BINAP as proposed by the catalytic cycle (Fig. 3). In protic solvents, the product can be released by both pathways, i.e. protonation by alcohol or by molecular hydrogen, while in aprotic solvents only protonation by molecular hydrogen is possible.

Addition of small amounts of water to methanol (5% (v/v)) to prevent acetal formation was previously published in literature. It led to a certain decrease in activity but no change in enantioselectivity [19]. Although water as a green and non-expensive protic solvent would seem to be a good alternative for methanol in heterogeneous reactions, it was found that the presence of water seriously hampered activity and enantioselectivity of the asymmetric reduction of MAA (Fig. 4). Both activity and enantioselectivity decreased with increasing amount of water. While the reduction in activity was very sharp even for small amounts added, the enantioselectivity remained stable up to 10 wt.% water in the system. As expected, no acetal was formed in the presence of water. The same effect of water on enantioselectivity was observed by Wan and Davis in the asymmetric synthesis of

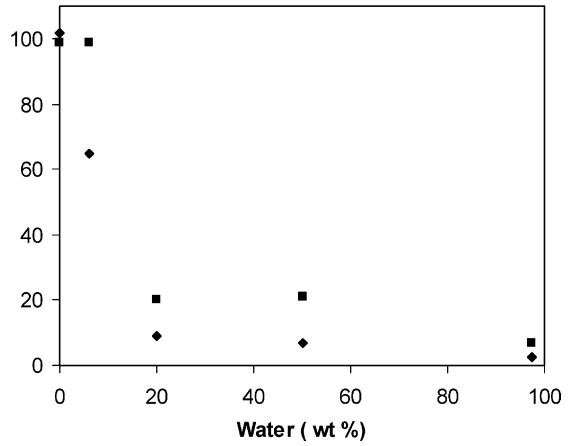


Fig. 4. The effect of water on activity and enantioselectivity. Reaction conditions: 60 °C, 40 atm $H_2$, 18 ml solvent, 2 g MAA, S/C = 3200, 3 h. (◆) TOF ($h^{-1}$); (■) ee (%).

Naproxen by Ru-BINAP complex heterogenized in a supported aqueous phase [31–33]. However, they reported a much smaller decrease in enantioselectivity with addition of water. The authors did not state whether the activity had changed. Hoke et al. found that the chloride ligand was essential for the enantioselectivity of the complex and replacement of the chloride ligand by [$PF_6$] resulted in the formation of a racemic product with no change in activity [17]. Wan and Davis suggested that the chloro ligand dissociates from the complex in water, leading to a changed complex configuration with decreased enantioselectivity.

The low activity in water could arise from several reasons. First, the absence of the chloro ligand might decrease the activity as well. Another possible explanation for the deactivation of the Ru-BINAP complex by water, is that water coordinates to the complex–substrate intermediate and transfers its proton to the product in step 6 (Fig. 3), leaving behind a hydroxyl group which coordinates so well that it simply blocks the complex. Obviously, the hydroxyl groups in water could deactivate the complex even before the beginning of the catalytic cycle.

## 3. Experimental

BINAP-chloro-(*p*-cymene)-Ru chloride complex was purchased from Fluka while MAA and all solvents were purchased from Across. Deuterated methanol was bought from Aldrich and deuterium was bought from Union Carbide Corporation.

A stainless steel reactor with magnetic stirring was used for all homogeneous reactions. First, the complex was dissolved in the reaction solvent (4–18 ml) and then the homogeneous mixture was added together with 0.1–0.5 g of MAA to the reactor. Reaction was carried out at 60 °C and a hydrogen pressure of 40–60 bar. The reactor was heated electrically and flushed with nitrogen followed by hydrogen 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.

For the GC/MS analysis, an instrument Fisons MD-800 with CP-Sil 5 CB column was used.

## 4. Conclusions

The asymmetric reduction of β-keto esters with Ru-BINAP is clearly highly solvent dependent and two different reaction pathways were proposed to explain this behavior. The reaction rate in alcoholic solvents is higher than in aprotic solvents. This is due to the protonation of the product by hydrogen transfer from the alcoholic solvent, which is faster than the protonation by gaseous hydrogen. Using relatively less acidic alcohols decreased the protonation of the product by the solvent. Non-linear alcohols poorly coordinate the complex, thus excluding hydrogen transfer from the solvent. Since no replacement of the hydride by the solvent was feasible either, the activity was even lower than in the chlorinated solvents. When water was added to the solvent, dissociation of the chloro ligand from the complex resulted in a decreasing enantioselectivity and activity.

## Acknowledgements

AW acknowledges a postdoctoral fellowship in the frame of the IAP-network in supramolecular chemistry and catalysis, sponsored by the Belgian Federal Government. The research is done in the same framework.

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