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Catalytic asymmetric hydrogenation of ethyltrifluoroacetoacetate with 4,4′ and 5,5′-*diam*BINAP Ru(II) complexes in unusual conditions

Mikaël Berthod [a], Gerard Mignani [b], Marc Lemaire [a,*]

[a] *Laboratoire de Catalyse et de Synthèse Organique, UMR 5181, UCBL, CPE Bat. 308, 43, Boulevard du 11 Novembre 1918, 69622 Villeurbanne Cedex, France*
[b] *Rhodia, Centre de recherches de Lyon, 85 avenue des Frères-Perret, BP 62, 69192 Saint-Fons Cedex, France*

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Abstract

The catalytic asymmetric hydrogenation of ethyltrifluoroacetoacetate with 4,4′ and 5,5′-*diam*BINAP-Ru(II) complexes was studied. An increased enantioselectivity was observed when hydrogenation was done in biphasic water/organic solvent conditions. Addition of acid increase the selectivity too. It was proposed an explanation based onto the keto-enol-hydrate or hemiketal equilibrium.

Keywords: Ethyltrifluoroacetoacetate; Hydrogenation; BINAP; Asymmetric catalysis

1. Introduction

The 4,4′, 5,5′, and 6,6′-BINAP derivatives and their ruthenium(II) complexes have been used in several different hydrogenation conditions. The solubility of such complexes in aqueous media [1], in ionic liquids [2] and for the perfluoroalkylated derivatives in supercritical carbon dioxide [3], allowed the use of a very large nature of media.

The trifluoroethylacetoacetate is a precursor of fluorous β-hydroxy esters which are interesting chiral groups use in the pharmaceutical industry for the synthesis of fluorous aminoacids [4], epoxydes [5], diols [6] or alcohol [7]. To our knowledge, an industrial asymmetric synthesis of ethyl-4,4,4-trifluoro-3-hydroxybutanoate **2** does not exist and the production of pure enantiomers is probably obtained by enzymatic or microbial resolution. Nevertheless, the asymmetric reduction of this substrate has been studied by several groups (Fig. 1).

Asymmetric hydrogenation of compound **1** with ruthenium catalysts does not give enough enantioselectivity for practical application. Noyori and co-workers [8] in 1988 obtained 46% ee using BINAP-ruthenium chloride as precursor, Sannicolo and co-workers [9] in 2000 obtained 85% ee using tetramethyl-BITIOP-ruthenium chloride, whereas Genêt and co-workers [10,11], whose undertook a whole study on this substrate, obtained from 23% ee with the BINAP up to 70% ee with an optimized ligand the difluorphos. They explained the increased performances of these catalysts by an improvement of the steric properties (dihedral angle) and electronic of the ligands. However, that does not explain why there is such a difference in selectivity between the ethylacetoacetate (99% ee with BINAP-$RuBr_2$) and the ethyltrifluoroacetoacetate. Miura and Tada [12], obtained compound **2** with 94.6% ee with asymmetrical hydrogen transfer catalyzed by ruthenium using a ligand previously developed by Noyori and co-workers [13].

Finally, the best results were obtained by Baiker et al. who carried out the hydrogenation of **1** and obtained compound **2** with 96% ee [14]. The system used was platine/alumine

* Corresponding author. Tel.: +33 47 243 1407; fax: +33 47 243 1408.
E-mail address: marc.lemaire@univ-lyonl.fr (M. Lemaire).

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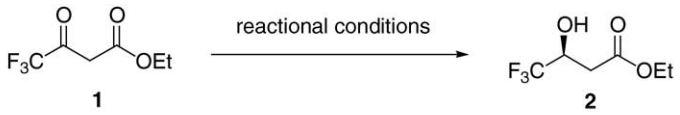


Groups	Reactional conditions	Yield (%)	ee (%)
Noyori [8] (1988)	RuHCl[(*R*)-BINAP]$_2$, 80 bars (H_2), 30°C EtOH	95	46
Sannicolo [9] (2000)	RuHCl[(*R*)-tetraMe-BITIOP]$_2$, 39 bars (H_2), 110°C EtOH	95	85
Genêt [10] (2000) (2003)	MeO-BIPHEP-RuBr$_2$, 10 bars (H_2), 99°C EtOH	100	42
	BINAP-RuBr$_2$, 10 bars (H_2), 99°C EtOH	100	23
	SYNPHOS-RuBr$_2$, 10 bars (H_2), 99°C EtOH	100	49
Genêt [11] (2004)	SEGPHOS-RuBr$_2$,10 bars (H_2), 110°C EtOH	100	59
	Difluorphos-RuBr$_2$, 10 bars (H_2), 110°C EtOH	100	70
Miura [12] (2002)	RuCl[(1R,2R)-p-TsNHCH(C_6H_5)CH(C_6H_5)NH_2](*p*-cymène), formic acid-triéthylamine, acétonitrile, 35°C	100	94.6

Fig. 1. Ethyltrifluoroacetoacetate asymmetric reduction with Ru(II) catalysts.

Table 1
Ethylacetoacetate keto-enol equilibrium in several solvents

Deuterated solvents	Enol form (%)	Keto form (%)
EtOH	12	88
MeOH	7.5	92.5
H_2O	6.5	93.5

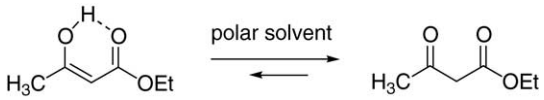
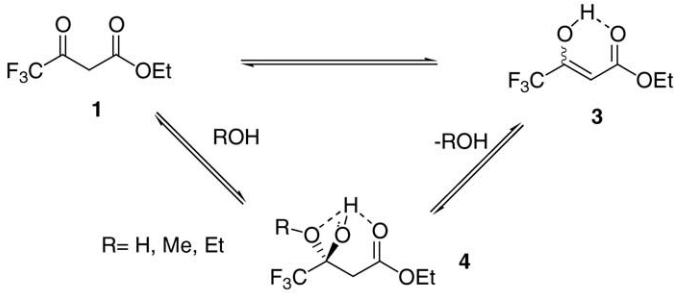


Fig. 2. The keto form of ethylacetoacetate predominates in polar solvents.

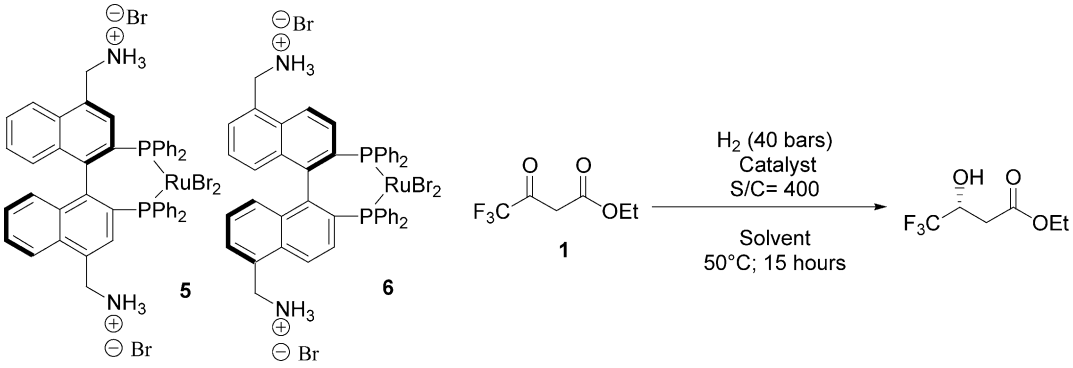
modified by *O*-methyl-cinchonidine in a mixture THF/AcOH (1:1) at 0 °C. The authors explain this selectivity by a protonation of the cinchonidine which forms a new complex. This complex allows a better enantioselection.

These results led us to seek viable conditions for which the ruthenium complexes formed with modified *diam*BINAP could be used for the asymmetric hydrogenation of ethyltrifluoroacetoacetate.



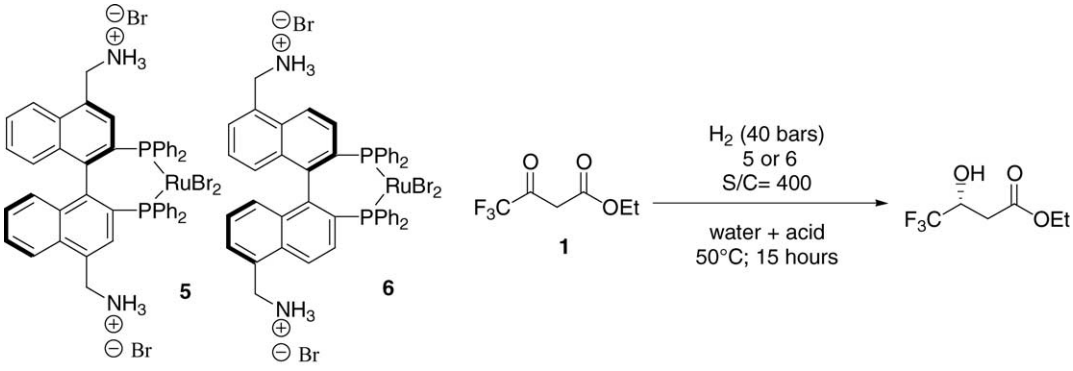
Deuterated solvents	Enol form(%) **3**	Keto form (%) **1**	Hydrate and hemiketal form (%) **4**
EtOH	10	2	88
MeOH	6	2	92
H_2O	11	5	84
Neat ester	90	10	0

Fig. 3. Ethyltrifluoroacetoacetate keto-enol-hydrate (or hemiketal) equilibrium in several solvents.



Entry	Catalyst	Solvent	Conversion (%)	ee (%)
1	(*R*)-BINAP-$RuBr_2$	Ethanol	100	23 (*R*)
2	(*R*)-4,4'-*diam*BINAP-$RuBr_2$	Ethanol	100	22 (*R*)
3	(*R*)-5,5'-*diam*BINAP-$RuBr_2$	Ethanol	100	20 (*R*)
4	**(*R*)-5**	Water	95	40 (*R*)
5	**(*R*)-6**	Water	95	41 (*R*)

Fig. 4. Hydrogenation of **1** in homogeneous media and in biphasic media water/organic solvent.



Entry	Catalyst	water (mL)	CH_3COOH (mL)	TFA (mL)	Conversion (%)	ee (%)
1	***(R)*-5**	1	0.25	0	90	57 *(R)*
2	***(R)*-5**	1	0	0.25	50	46 *(R)*
3	***(R)*-5**	1	0.25	0.25	80	65 *(R)*
4	***(R)*-5**	1	0.125	0.125	95	70 *(R)*
5	***(R)*-5**	0	0.25	0.25	0	0
6	***(R)*-6**	1	0.25	0	88	55 *(R)*
7	***(R)*-6**	1	0	0.25	45	47 *(R)*
8	***(R)*-6**	1	0.125	0.125	93	67 *(R)*
9	***(R)*-6**	0	0.25	0.25	0	0

Fig. 5. Hydrogenation of **1** in biphasic media water/organic solvent with addition of acid.

2. Results and discussion

2.1. Ethyltrifluoroacetoacetate keto-enol equilibrium

In order to understand the selectivities differences observed in the hydrogenation of ethylacetoacetate and ethyltrifluoroacetoacetate with the BINAP-Ru(II) catalyst we try to focused on the species which can be in the mixture during the hydrogenation. For the ethylacetoacetate in solution in ethanol, methanol or water the keto form predominate over the enol form [15] (Table 1).

In this case, the solvent must favorized the keto ester by intramolecular hydrogen bond formation to the detriment of the cyclic enol form (Fig. 2) [10].

For the β-ketoester **1**, the equilibrium is more complicated because of emergence of hydrate or hemiketal forms [16] **4** (Fig. 3).

In this case the hydrate or the hemiketal forms predominate. With the trifluoromethyl group the carbon of the carbonyl is much more electrophile and then much sensitive to the hydration or hemiketalisation. Moreover, forms **4** are stabilized by the possibility of formation of two hydrogen bonds [17].

2.2. Ethyltrifluoroacetoacetate hydrogenation with 4,4′ and 5,5′-diamBINAP-RuBr$_2$

Firstly compound **1** has been hydrogenated in ethanol with 4,4′ and 5,5′-*diam*BINAP-RuBr$_2$. With no surprise, total conversions and low ee were obtained as Genêt described with BINAP as ligand [10] (Fig. 4).

No positive effects were observed on selectivity using *diam*BINAP instead of BINAP. Other tests have been realized in supercritical carbon dioxide, in hexafluoropropanol or in ionic liquids but no better results have been obtained so far.

The β-ketoester **1** has been hydrogenated in a biphasic system water/organic solvent with modified 4,4′ and 5,5′-*diam*BINAP-RuBr$_2$ (**5**, **6**) hydrosoluble catalysts already described. In these conditions total conversion and 40% ee were obtained with both catalysts (Fig. 4).

As we have shown same ligand could give differents selectivity whether they were used in a media or another.

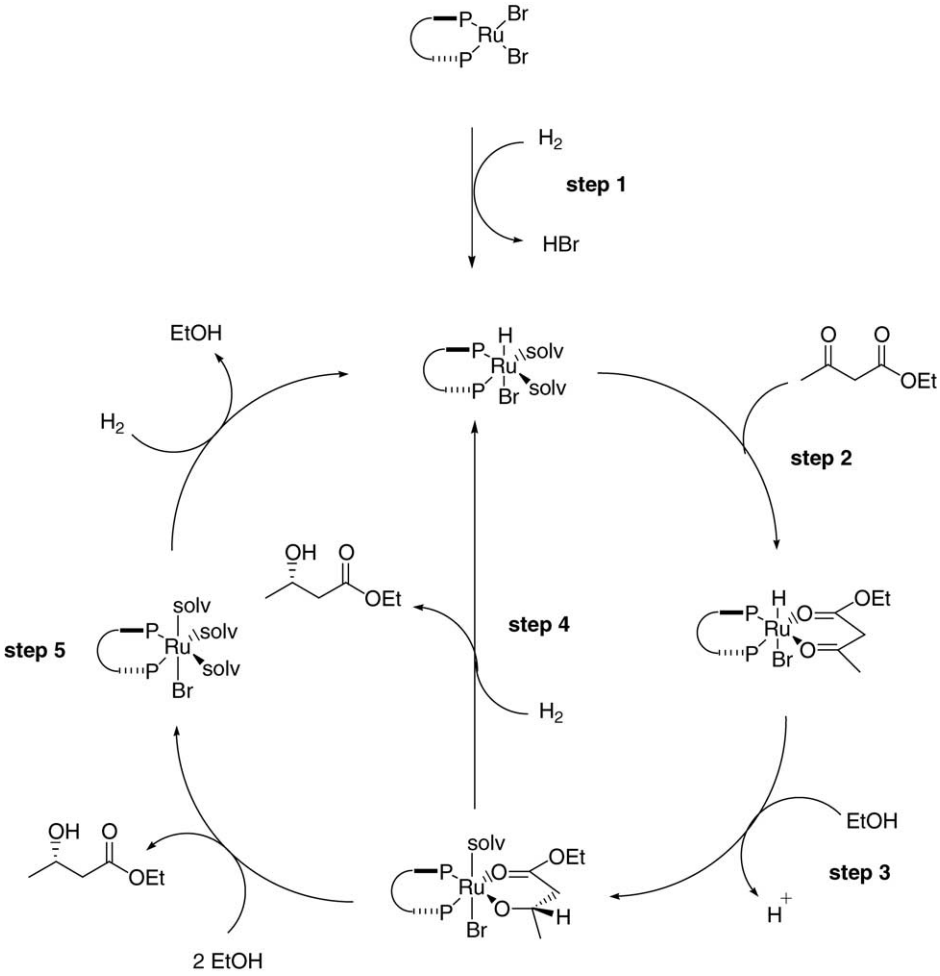


Fig. 6. Catalytic cycle for enantioselective hydrogenation of ethylacetoacetate with BINAP-RuBr$_2$ catalysts.

As we have seen the keto-enol-hydrate (or hemiketal) equilibrium could change too. In order to modify this equilibrium the media were acidified. Unfortunately when organic or inorganic acid were added in the alcohol media the catalysts precipitated. Nevertheless, in water it was possible to have an efficient system. Substrate **1** was then hydrogenated in biphasic conditions water/organic solvent with addition of acetic acid and/or trifluoroacetic acid (Fig. 5).

In each case addition of acid increased the selectivity. Good conversion were obtained except when only TFA was added (entry 2 and 7). In these cases undefined byproducts was obtained. Without water the catalysts precipitated and became inefficient (entry 5 and 9). The best results were obtained with a mixture water (1 mL) + acetic acid (0.125 mL) + trifluoroacetic acid (0.125 mL). 70% and 67% ee were obtained with **5** and **6** (entry 4 and 8). In our knowledge, these are among the best results obtained for the reduction of ethyltrifluoroacetoacetate BINAP-ruthenium(II) catalysts. The mechanism of asymmetric hydrogenation of ethylacetoacetate with Ru-BINAP complexes has already been described [18] (Fig. 6).

According to this mechanism, it is the keto form which was complexed and then reacted to give the product. For the ethyltrifluoroacetocatetate the keto form does not predominate in the alcohol. Baiker et al. have shown that a competition between hydrogenation of **1** and hydrogenolyse of **4** occurs [19]. Nevertheless, addition of acid for the asymmetric hydrogenation of methylacetoacetate with the BINAP-chloro-(*p*-cymene)-Ru chloride complex increased activities while enantioselectivity remained almost unchanged [20]. The authors explained this phenomena by an easiest hydride insertion (step 3) and a substrate protonation before the hydride insertion which speed up this step (Fig. 7).

We suppose the mechanism is the same with ethyltrifluoroacetoacetate in alcohol or in water. Then, the selectivity could be explain by the change in the keto-enol-hydrate or hemiketal equilibrium. Indeed, Baiker et al. have shown recently that hydrogenolysis of hydrate form is orders of magnitude slower than hydrogenation of the keto form of ethylacetoacetate [21]. The acidic medium increase the speed of the equilibrium and then in our case could change this one in direction of the keto form. So by speed up the hydrogenation of the keto form and speed up the keto-enol-hydrate or hemike-

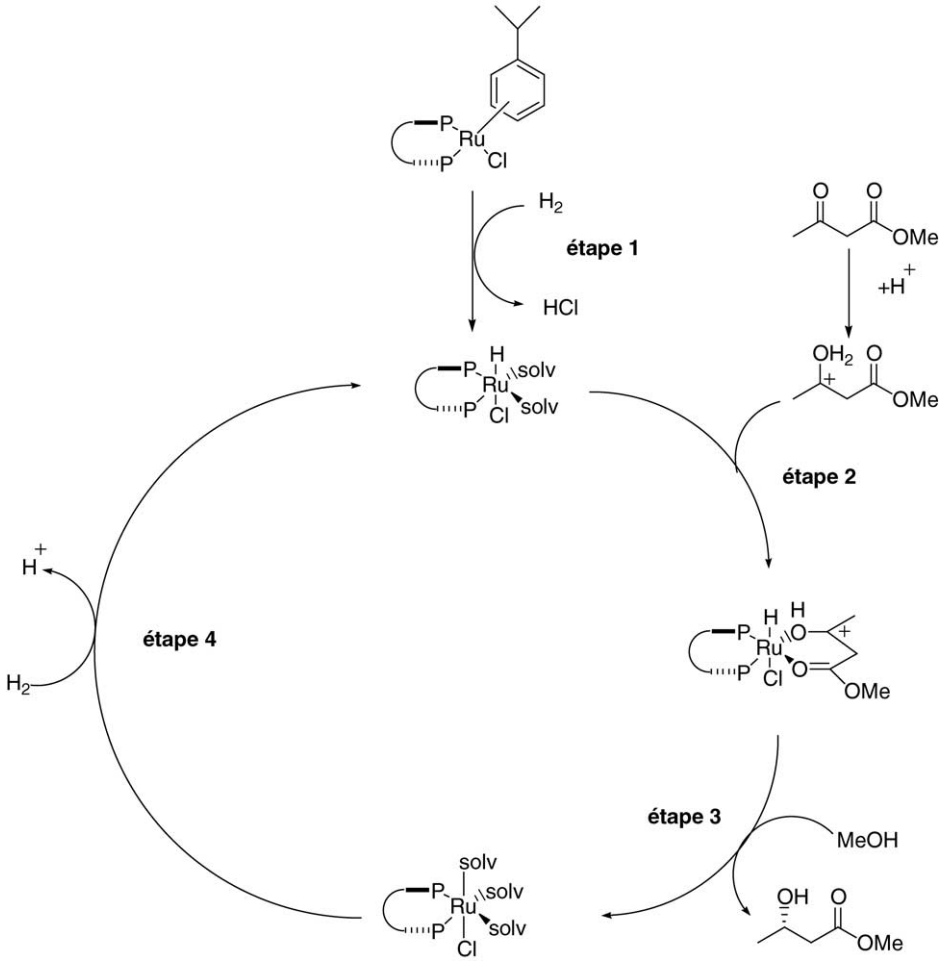


Fig. 7. Catalytic cycle for enantioselective hydrogenation of methylacetoacetate with BINAP-$RuCl_2$(*p*-cymene) catalysts with addition of acid.

tal equilibrium, we suppose that we are able to influence the selectivity of hydrogenation of ethyltrifluoroacetoacetate.

3. Conclusion

We shown that the water-soluble catalysts derived from the 4,4′ and 5,5′- *diam*BINAP could be used under unusual solvent conditions. These catalysts made it possible to study the hydrogenation of the ethyltrifluoroacetoacetate in acid medium. This system led to one of the best enantioselectivities (70% ee i.e. an increase of 47% ee) obtained with a catalyst with the ruthenium(II) complexed by the BINAP or one of its derivatives. We have shown finally that with this kind of robust catalysts, news and many reactional possibilities are offered to us.

4. Experimental

4.1. Formation of the catalysts

The 4,4′ and 5,5′-diamBINAP-$RuBr_2$ was prepared as described in the literature [1].

4.2. Typical reduction procedure of ethyltrifluoroacetoacetate in ethanol

All experiments were performed under argon and all solvents were degassed by argon bubbling followed by three vacuum/argon cycles. A calculated amount of ethyl trifluoroacetoacetate in 2 mL of EtOH was added to the above catalysts obtained in situ (substrate/cat = 400). This solution was put in a stainless steel hydrogenation vessel. After purging three times with argon and three times with hydrogen, the pressure was raised to 40 bars and the reaction mixture stirred at 50 °C for 15 h. The reaction mixture was filtered on Celite and analyzed by GC to determine both conversion and ee. GC conditions for the ethyltrifluoroacetoacetate: Column Lipodex A (25 m × 0.25 mm) 45 °C (5 min) 1 °C/min −60 °C (5 min); enantiomers (26.2 and 26.7 min); starting material (12.1 min).

4.3. Typical biphasic reduction procedure of ethyltrifluoroacetate in water and acid

Under Ar, to the catalysts dissolved in H_2O (1 mL), the water-insoluble ethyltrifluoroacetoacetate were added (substrate/catalyst: 400). A calculated quantity of acid (acetic acid or/and TFA) was then added. This biphasic mixture was allowed to stir and then stand overnight in a stainless steel hydrogenation vessel at 50 °C under 40 bar H_2. The resulting water-soluble reduced product was extracted three times with pentane.

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