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# Enantioselective hydrogenation of isomeric β-acetamido β-alkylacrylates: crucial influence of temperature

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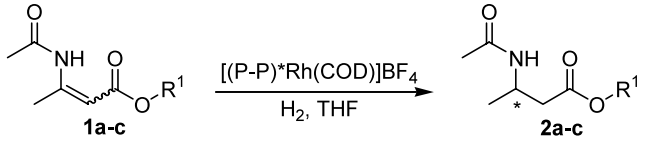
**Abstract**—The hydrogenation of β-acylaminoacrylate with [((*R*,*R*)-Et-BPE)Rh(COD)]$BF_4$ and [((*S*,*S*)-Et-Duphos)Rh(COD)]$BF_4$, reveals an important temperature effect. With each ligand, under the best experimental conditions, the β-acylamino ester **2b** was isolated in 93–94% e.e. from a 1:1 mixture of (*E*/*Z*) ethyl β-acylaminoacrylate **1b**. © 2003 Elsevier Science Ltd. All rights reserved.

## 1. Introduction

Homochiral β-amino acids are important targets in pharmaceutical industry as they are useful functional building blocks for the synthesis of β-lactams, β-peptides, antibiotics and drugs.[1] Their preparation in enantiomerically pure form has become a challenge for organic chemists in recent years.[2] The main approaches for stereoselective synthesis of β-amino acids are based on homologation of α-amino acids,[3] enzymatic resolution,[4] enolate addition to imines,[5] Curtius rearrangements,[6] conjugate addition of nitrogen nucleophiles to α,β-unsaturated derivatives,[7] aminohydroxylation[8] and β-lactam synthesis.[9] However, the most promising method for a large scale preparation of enantiomerically pure β-amino acids appears to be the catalytic asymmetric hydrogenation of β-acetamidoacrylates, which involves clean atom economical reactions and offers the preparation of both (*R*)- and (*S*)-enantiomers.

The early examples gave modest enantiomeric excesses[10] and the first breakthrough came with the use of Noyori's Binap-ruthenium catalytic systems,[11] which led to 96% enantiomeric excess from the (*E*)-isomer, but only to 5% e.e. from the (*Z*)-isomer. More recently, new efficient chiral diphosphine- and monophosphoramidite-metal complexes were used as catalysts for the asymmetric hydrogenation of β-acetamidoacrylates, and good enantiomeric excesses were obtained with rhodium(I)[11–16] and with ruthenium(II) complexes.[17,18] Some of these new catalytic systems are very efficient for the hydrogenation of both isomeric substrates,[14,15] but it is still a challenge to achieve this hydrogenation in good yield and high enantiomeric excess from the pure (*Z*)-isomer and the crude mixture of (*Z*)- and (*E*)-isomers resulting from their preparation from β-ketoesters.

In our ongoing effort to prepare optically active amines such as aminochromanones and aminotetralines via asymmetric hydrogenation,[19–23] it appeared that subtle modifications of conditions and substrates led to big improvements in enantiomeric excess. The enantioselective hydrogenation of β-acetamidoacrylates **1a–c** with the aim of producing β-aminoesters in high enantiomeric excesses was then studied (Scheme 1).




**a**: $R^1$= Me, **b**: $R^1$= Et, **c**: $R^1$= *t*Bu

**Scheme 1.**

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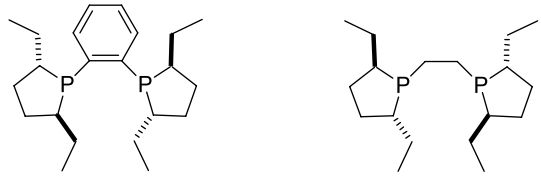
We report here a study focused on the enantioselective hydrogenation of (*E*), (*Z*) and (*E*)/(*Z*) mixtures of β-acetamidoacrylates in the presence of rhodium(I) catalysts in THF under low hydrogen pressure. We demonstrate that the enantioselectivity of the hydrogenation is highly temperature dependent and that [(BPE)Rh(COD)]$BF_4$ leads to β-acetamidobutanoate **2** in high enantiomeric excess from a (*E*)/(*Z*)-**1** mixture under selected conditions.

Our first attempts to hydrogenate methyl β-acetamidoacrylate (*Z*)-**1a** with chiral ruthenium complexes were unsuccessful as ((*R*)-Binap)Ru$(OCOCF_3)_2$ or an in situ generated '((*R*,*R*)-Me-Duphos)Ru' precursor[22,23] led to enantioselective excesses up to only 29% under high hydrogen pressure (100 bars). By contrast, the rhodium analogues gave better results and we focused our work on the hydrogenation of **1a**–**b** in the presence of rhodium catalysts with (*S*,*S*)-Et-Duphos and (*R*,*R*)-Et-BPE (Scheme 2) as ligands.




(*S*,*S*)-Et-Duphos (*R*,*R*)-Et-BPE

**Scheme 2.**

## 2. Hydrogenation with Et-Duphos as ligand

The prochiral derivatives **1a**–**c** were prepared by reaction of ammonium acetate with the appropriate β-ketoester followed by acylation of the amino group.[11] A mixture of (*Z*) and (*E*) stereoisomers was obtained with this procedure, but both isomers could be isolated in pure form via recrystallization techniques. The hydrogenation was carried out with 0.5 mmol of substrate, 1 mol% of catalyst [(P-P)*Rh(COD)]$BF_4$ in 5 ml of degassed THF, under an initial hydrogen pressure of 2 bars for 1 h. In all experiments, quantitative conversions were obtained. It is noteworthy that in THF at room temperature, Et-Duphos always gave better results than Me-Duphos in terms of enantioselectivity. Thus for (*E*)-**1a**, 73% enantiomeric excess was obtained with Me-Duphos and 95% e.e. with Et-Duphos. Such a difference was not observed in methanol, where both ligands gave high e.e.'s (98.2 and 97%, respectively).[12b] In THF, the presence of (*S*,*S*)-Et-Duphos as the chiral ligand led to the formation of the (*S*)-**2a**–**b** enantiomers from **1a**–**b**, and the (*Z*)-isomer exhibited a lower reactivity and selectivity than the (*E*)-isomer.

The hydrogenation of (*E*)-**1a**, (*Z*)-**1a** and a 1/1 mixture of (*E*) and (*Z*)-**1a** with [((*S*,*S*)-Et-Duphos)-Rh(COD)]$BF_4$ as catalyst revealed a strong influence of the reaction temperature (Fig. 1).

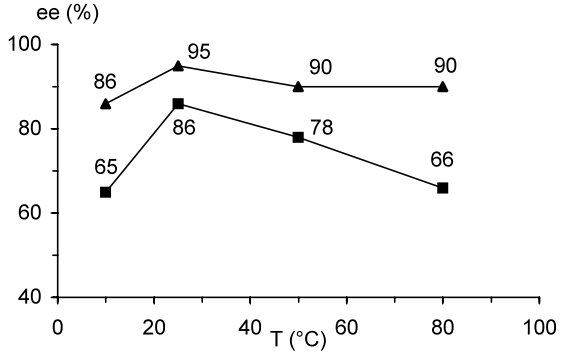



**Figure 1.** Hydrogenation of 0.5 mmol of compound **1a** with 1 mol% of [((*S*,*S*)-Et-Duphos)Rh(COD)]$BF_4$ as catalyst under 2 bars of hydrogen for 1 h in 5 mL of degassed THF. ■ (*Z*)-isomer, ▲ (*E*)-isomer.

Whatever the reaction temperature, the e.e.'s of **2a** resulting from the hydrogenation of the (*E*)-isomer are higher than those arising from the (*Z*)-isomer (for example at 25°C, (*E*)-**1a** provided **2a** in 95% e.e. whereas under the same conditions **2a** is obtained in 86% e.e. from (*Z*)-**1a**). In the case of a mixture of (*E*/*Z*)-isomers, when the reaction was not complete, only unreacted (*Z*)-**1a** was detected. This observation contrasts with the results observed during the hydrogenation of β-acylacetamidoacrylate in methanol.[12d] It is noteworthy that the temperature has a stronger effect on the enantioselectivity obtained from (*Z*)-**1a** than from the (*E*)-isomer. For both isomers, the enantioselectivity of the hydrogenation in THF presents a maximum at 25°C, which is not observed in methanol.[12d] From these results, it appeared that 25°C under 2 bars of hydrogen represents the best conditions in THF with [Rh((*S*,*S*)-Et-Duphos)(COD)]$BF_4$ as catalyst precursor, for the hydrogenation of **1a**. Under these conditions, **2a** was obtained in 90% e.e from a (1:1) (*E*)-(*Z*) **1a** mixture.

In order to evaluate the influence of the nature of the ester group on the enantioselectivity of the hydrogenation, the nature of the $R^1$ group was varied. With ethyl ester **1b**, the temperature effect was not as important as with methyl ester **1a** (Fig. 2). Indeed, the enantiomeric

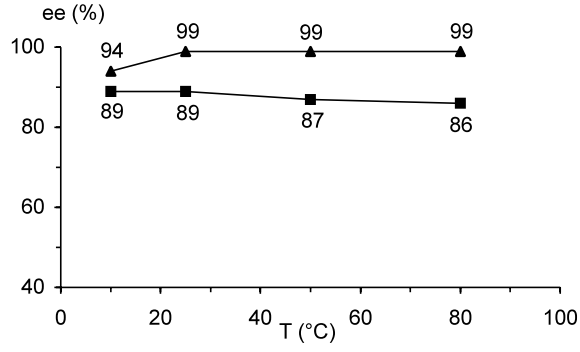



**Figure 2.** Hydrogenation of 0.5 mmol of compound **1b** with 1 mol% of [((*S*,*S*)-Et-Duphos)Rh(COD)]$BF_4$ as catalyst under 2 bars of hydrogen for 1 h in 5 mL of degassed THF. ■ (*Z*)-isomer, ▲ (*E*)-isomer.

excesses resulting from the (*E*)-**1b** isomer as prochiral substrate increased between 10 and 25°C (from 94 and 99%) and then remained constant up to 80°C. For the (*Z*)-**1b** isomer, the temperature had little effect. The highest values (89% e.e.) were obtained in the range 10–25°C and there was only a slight decrease between 25 and 80°C. Moreover, these results clearly showed that the ethyl ester **1b** provided better enantioselectivities compared to the methyl ester **1a**. Here again for a 1:1 mixture of (*E*)/(*Z*) isomers, the most favorable temperature is 25°C. Corresponding to the expected average value, compound (*S*)-**2b** was obtained in 94% e.e. from a 1:1 mixture of (*E*) and (*Z*)-**1b** isomers at 25°C.

## 3. Hydrogenation with Et-BPE as ligand

In order to examine the influence of the nature of the bridge linking both phospholanes, compounds **1a** and **1b** were also hydrogenated in THF under 2 bars of hydrogen at different temperatures with (*R*,*R*)-Et-BPE as chiral ligand. This ligand led to the formation of (*S*)-**2a**–**b** as major isomers.

As described in Figure 3, the selectivity of the hydrogenation of (*Z*)-**1a** showed a strong temperature dependency. An increase of 24% of the enantiomeric excess was observed going from 10°C to 40°C. In sharp contrast with the results observed in methanol or THF with Et-Duphos, the best e.e. was observed at 40°C (82% e.e.). A slight decrease of e.e.'s was observed at higher temperature above 40°C. With the (*E*)-**1a** isomer, the temperature effect was not as important as with the (*Z*)-**1a** isomer and only a slight decrease was noticed above 40°C (from 98 to 94% e.e., Fig. 3).

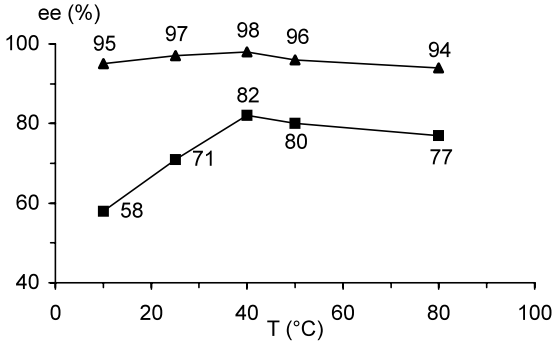



**Figure 3.** Hydrogenation of 0.5 mmol of compound **1a** with 1 mol% of [((*R*,*R*)-Et-BPE)Rh(COD)]$BF_4$ as catalyst under 2 bars of hydrogen for 1 h in 5 mL of degassed THF. ■ (*Z*)-isomer, ▲ (*E*)-isomer.

The influence of temperature was more drastic during the hydrogenation of (*Z*)-**1b** (Fig. 4). Whereas, **2b** was isolated in only 43% e.e. from the hydrogenation carried out at 10°C, an enantiomeric excess of 90% was obtained at 40°C. As also noticed with Et-Duphos (Fig. 2), (*E*)-**1b** gave **2b** in very high enantiomeric excesses (98–99%) in a large range of temperature (20–50°C).

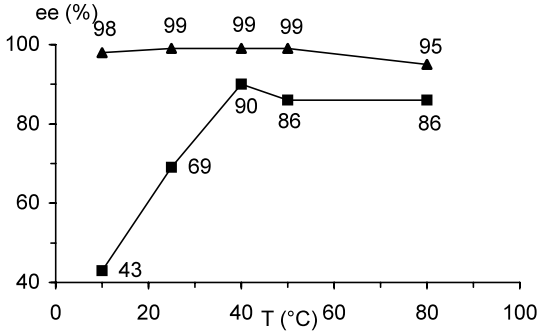


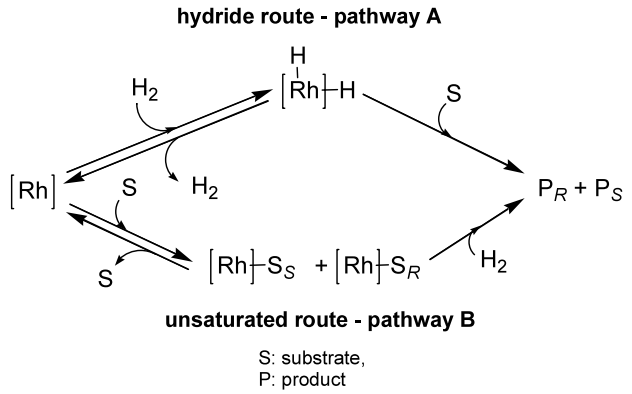

**Figure 4.** Hydrogenation of 0.5 mmol of compound **1b** with 1 mol% of [((*R*,*R*)-Et-BPE)Rh(COD)]$BF_4$ as catalyst under 2 bars of hydrogen for 1 h in 5 mL of degassed THF. ■ (*Z*)-isomer, ▲ (*E*)-isomer.

Finally, the optimum temperature required for the enantioselective hydrogenation of β-acetamidoacrylates **1a** and **1b** with [Rh((*R*,*R*)-Et-BPE)(COD)]$BF_4$ as pre-catalyst is around 40°C. As also observed with Et-Duphos as chiral ligand, the ethyl ester **1b** leads to better results in terms of enantioselectivity than the methyl ester **1a**. However, increasing the steric hindrance of the ester (compound **1c**, $R^1 = t$Bu) did not lead to further improvement of the enantiomeric excesses. Thus, 67% e.e. and 72% e.e. were obtained from compound **1c** with Et-Duphos at 25°C and Et-BPE at 40°C, respectively. These reaction conditions make possible the hydrogenation of the β-acetamidoacrylate (*Z*)-**1b** to provide **2b** in good e.e.'s (up to 90%), which represents the best e.e. ever reported with a BPE ligand. It is noteworthy that this hydrogenation with Et-BPE is one of the rare examples that provided high e.e. at elevated temperature. Applying the optimised conditions made possible the preparation of compound **2b** in 93% e.e. from a 1:1 mixture of both stereoisomers **1b** and **2a** in 89% e.e. from a 1:1 mixture of both stereoisomers **1a**.

## 4. Discussion

The pronounced improvement of the enantiomeric excess by increasing the reaction temperature, is quite rare in hydrogenation even if some examples are known in other catalytic reactions,[24] since it has been generally accepted that the higher the temperature, the lower the enantioselectivity at a given hydrogen pressure. To the best of our knowledge, only two examples of such a behaviour were previously reported in the literature during the hydrogenation of α-dehydroamino acid derivatives,[25,26] but it was not observed from β-acetamidoacrylates above room temperature.[12d]

In contrast with the α-dehydroacetamido esters,[27] there is still no model for the reaction sequence involved in the enantioselective hydrogenation of β-dehydroacylamino esters. In the work reported by Grydnev and Imamoto,[13] NMR evidences demonstrated an 'hydride route' (**A**) (Scheme 3). A second mechanism (**B**), which proceeds via first coordination of the substrate, was




**Scheme 3.**

found to be more appropriate to explain the results obtained in methanol with Et-Duphos as chiral ligand.[12d]

We have observed that in THF with (*R*,*R*)-Et-BPE as chiral ligand, e.e.'s are strongly affected by the experimental pressure (going up from 2 to 10 bars led to a decrease from 90 to 48% e.e. at 40°C and from 69 to 32% e.e. at 25°C from (*Z*)-**1b**). As in the hydride route (**A**), the enantiomeric excesses are independent of the applied pressure,[12d] we assumed that the hydrogenation in THF mainly proceeds via the route (**B**) whatever the temperature. But we have yet no evidence to explain why e.e.'s are better with Et-BPE at 40°C in THF compared to Et-Duphos, which provided the best results in THF or in methanol at room temperature from compound (*Z*)-**1**. The only differences between the two systems are the following: i) BPE possesses a more flexible bridge linking the two phospholane units; ii) the intramolecular hydrogen bonding in compound (*Z*)-**1** is always efficient in THF, which is not the case in methanol, as seen by $^1$H NMR experiments at different temperatures (25–70°C). One explanation for the improvement of the enantioselectivity during the hydrogenation of compounds (*Z*)-**1** with Et-BPE at 40°C might be a more favorable interaction between the rigid prochiral olefin and the phospholane units due to the higher flexibility of the ligand at more elevated temperature.

In conclusion, we have shown that temperature has a strong influence on the enantioselectivity of the hydrogenation of β-acetamidoacrylates, especially for the (*Z*)-isomers under low pressure of hydrogen in THF with Et-BPE as chiral ligand. This fact confirms that temperature screening must be carried out for hydrogenation reactions to reach the best enantiomeric excess. Under the best experimental conditions, Et-BPE competes with Et-Duphos[12] and BDMPI,[15] and makes the preparation of compound **2b** in 94% e.e. possible from a 1:1 mixture of both stereoisomers **1b**. The pressure and temperature effects seem to indicate that the hydrogenation of β-acylacetamidoacrylate, in the presence of Et-Duphos or Et-BPE ligands, follows the unsaturated route (**B**) in THF.

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