Rh-Catalyzed asymmetric hydrogenation of (*Z*)-ethyl 3-acetamido-2-butenoate in supercritical carbon dioxide: the effect of cosolvents

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Rh-Catalyzed asymmetric hydrogenation (up to 85% *ee*) of (*Z*)-ethyl 3-acetamido-2-butenoate was carried out for the first time in supercritical CO_2 using protic cosolvents. The activity of the Rh catalyst bearing the amidophosphite ligand increases with an increase in acidity of the protic cosolvents and with hydrogen pressure.

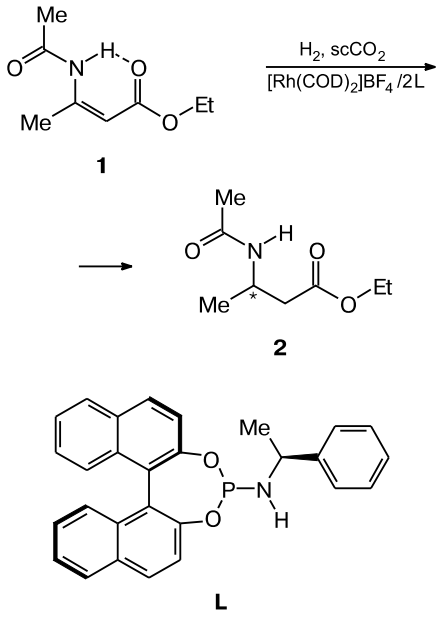
Key words: amidophosphites, hydrogenation, rhodium, (*Z*)-ethyl 3-acetamido-2-butenoate, supercritical carbon dioxide, cosolvents.

Supercritical carbon dioxide ($scCO_2$) is an available, uninflammable, and ecologically friendly solvent. Many organic reactions are carried out presently in this solvent. The properties of $scCO_2$ vary, to a considerable extent, with pressure and temperature and upon the addition of a small amount of cosolvents. All these factors can affect the rate and selectivity of reactions.[1—3] Among the reactions catalyzed by transition-metal complexes, asymmetric hydrogenation can be distinguished, which is characterized by the use of of molecular hydrogen as the cheapest reducing agent and low loadings of the catalyst (≤1 mol.%).[4]

The known examples for asymmetric hydrogenation by metal complexes using $scCO_2$ as a reaction medium are mainly related to the application of chiral phosphine ligands.[3] We have recently shown that synthetically available chiral phosphites and amidophosphites represent a more promising class of ligands for asymmetric hydrogenation in $scCO_2$, since in their presence the reaction occurs with a high rate and enantioselectivity.[5—10] The reaction product is classified as a derivative of unnatural β-amino acids used as antibiotics and antifungal drugs, as well as for the synthesis of β-peptides with enhanced resistance to enzymes.[11,12]

In this work we present the results of asymmetric hydrogenation of (*Z*)-ethyl 3-acetamido-2-butenoate (**1**, Scheme 1), which was carried out for the first time in $scCO_2$ and aimed at preparing the derivative of the corresponding β-amino acid. The influence of cosolvents on the conversion and enantioselectivity of the process were also studied.

Scheme 1



COD is 1,5-cyclooctadiene

Results and Discussion

In preliminary experiments we studied the hydrogenation of compound **1** in $scCO_2$ at 50 °C using the catalyst formed *in situ* from $[Rh(COD)_2]BF_4$ and amidophosphite **L** in CH_2Cl_2 followed by solvent removal *in vacuo* (see

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Experimental). However, no reaction occurred bellow a hydrogen pressure of 40 atm and a total pressure in the reactor of 150—200 atm. Evidently, the strong hydrogen bond in compound **1** between the amidic proton and the hydrogen atom of the carboxyl group (see Scheme 1) prevents the coordination of the C=O groups to the rhodium atom and impedes hydrogenation, which involves, according to the commonly known mechanism, both the C=C and C=O centers.[13—16]

Thus, 1,1,1,3,3,3-hexafluoro-2-propanol (hexafluoroisopropanol) was added to the catalytic system. This polar organic protic solvent makes it possible to cleave hydrogen bonds in amides and esters.[17,18] Indeed, with the use of this cosolvent in the hydrogenation of compound **1** by the catalytic system $[Rh(COD)_2]BF_4/2\mathbf{L}$ in $scCO_2$ at 50 °C using H_2 (40 atm) and a total pressure of 150 atm we were able to achieve 85% conversion and 76% *ee* for 3 h. A decrease in the hydrogen pressure from 40 to 20 atm decreased conversion and enantioselectivity (Table 1, entry *4*). An increase in carbon dioxide pressure from 150 to 200 atm also decreased conversion; however, enantioselectivity remained unchanged (see Table 1, entries *3* and *5*). The best result (conversion 100%, 85% *ee*) was achieved under a total pressure of 100 atm (see Table 1, entry *6*). In order to study the temperature effect, the reaction was carried out at 40 °C using H_2 (40 atm) and a total pressure of 100 atm; however, a low conversion and 75% *ee* were obtained (see Table 1m entry *7*). When the reaction was carried out in hexafluoroisopropanol (1.5 mL) in the absence of CO_2, with a 50% conversion for 3 h (50 °C, P_{H_2} = 40 atm) the enantiomeric excess was 47% (see Table 1, entry *8*).

The use of non-fluorinated alcohols, *viz.*, isopropyl and *tert*-butyl alcohols, as cosolvents in the hydrogenation of compound **1** gave no good results: for 3 h 0—13% conversion and 36—50% *ee* (see Table 1, entries *9—12*) were achieved. It is most likely that these data are explained by the fact that these alcohols are inferior to hexafluoroisopropanol in acidity. However, it can be mentioned that a higher enantioselectivity was obtained in the presence of more sterically bulky *tert*-butyl alcohol (see Table 1, entries *10* and *12*). For hydrogenation using P_{H_2} = 20 atm, the conversion and *ee* of reaction product **2** were low; however, an increase in the hydrogen pressure to 40 atm sharply increased the conversion and enantioselectivity of the process under other equivalent reaction conditions (see Table 1, entries *13* and *14*). The positive influence of the acidity of the cosolvent on the hydrogenation rate of substrate **1** in $scCO_2$ was confirmed by the results of experiments in the presence of acetic acid (P_{H_2} = 40 atm). In this case, at 50 °C and a total pressure of 100 and 150 atm, quantitative conversion and 77% *ee* are observed in 3 h (see Table 1, entries *15* and *16*).

Thus, for the first time we succeeded to carry out the asymmetric metallocomplex hydrogenation of precursors of unsaturated β-amino acids in $scCO_2$ using the protic cosolvents. It was found that the hydrogenation rate increased with an increase in the acidity of the cosolvents, and an increase in the hydrogen pressure also favors the enhancement of enantioselectivity and conversion.

Table 1. Rh-Catalyzed asymmetric hydrogenation of (*Z*)-ethyl 3-acetamido-2-butenoate (**1**)[a]

Entry	P_{H_2}	P_{tot}[b]	*T*/°C	Cosolvent	Conversion	*ee*[c]
	atm				%	
1	40	150	50	—	0	—
2	40	200	50	—	0	—
3	40	150	50	$HOCH(CF_3)_2$	85	77
4	20	150	50	$HOCH(CF_3)_2$	27	60
5	40	200	50	$HOCH(CF_3)_2$	50	77
6	40	100	50	$HOCH(CF_3)_2$	100	85
7	40	100	40	$HOCH(CF_3)_2$	24	75
8	40	—	50	$HOCH(CF_3)_2$	50	47
9	20	150	50	Pr^iOH	13	36
10	40	150	50	Pr^iOH	8	40
11	20	150	50	Bu^tOH	0	—
12	40	150	50	Bu^tOH	8	50
13	20	150	50	MeOH	21	16
14	40	150	50	MeOH	86	71
15	40	100	50	AcOH	100	77
16	40	150	50	AcOH	100	77

[a] Duration of hydrogenation 3 h.
[b] Total pressure.
[c] (*S*)-Configuration in all cases.

Experimental

(*Z*)-Ethyl 3-acetamido-2-butenoate (**1**), (R_a,S_c)-2-(1-phenylethylamino)dinaphtho[2,1-*d*:1′,2′-*f*][1,3,2]dioxaphosphepane (**L**), and $[Rh(COD)_2]BF_4$ were synthesized according to the procedures described previously.[13,19,20] The spectral data for ethyl 3-acetamidobutanoate (**2**) agree with the published data.[13]

Asymmetric hydrogenation of (*Z*)-ethyl 3-acetamido-2-butenoate (1) (general procedure). A mixture of $[Rh(COD)_2]BF_4$ (2 mg, 0.005 mmol) and ligand **L** (4.3 mg, 0.01 mmol) was placed in a 10-mL autoclave and dissolved in 0.3 mL of CH_2Cl_2. The reaction mixture was stirred for 2 min, the solvent was removed *in vacuo*, and enamide **1** (103 mg, 0.6 mmol) and a cosolvent (0.3 mL) were added. The closed autoclave was purged with CO_2 and filled with hydrogen to a necessary pressure and then with carbon dioxide using a manually operated pump (High Pressure Equipment). The reactor was heated to the corresponding temperature for 5 min, and experiments were carried out with magnetic stirring. After the end of the reaction, CO_2 and H_2 were separated from the reaction mixture, which was analyzed by ^{1}H NMR spectroscopy. The optical yields of compound **2** were determined by HPLC on an Agilent HP-1100 chromatograph using a Chiralcel OJ-H column (UV, $\lambda = 219$ nm, C_6H_{14}—Pr^iOH (95 : 5), 1 mL min^{-1}). The retention times for enantiomers of **2** were 11.5 ((*S*)-isomer) and 12.5 min (*R*), and that for enamide **1** it was 8.1 min. The absolute configurations of the enantiomers of **2** were established by comparing the results of measurements of optical rotation with the literature data.[21]

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