Asymmetric hydrogenation of methyl (*Z*)-2-acetamido-3-(3,4-dimethoxyphenyl)acrylate catalyzed by Rh complexes with available amidophosphite ligands

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A convenient express procedure for the preparation of methyl (*Z*)-2-acetamido-3-(3,4-dimethoxyphenyl)acrylate was developed. Asymmetric hydrogenation of this substrate in the presence of rhodium catalysts involving synthetically available amidophosphite ligands was carried out, which is characterized by high enantioselectivity (to 99.5% *ee*) and complete conversion. An approach to the selective formation of cationic complexes containing two ligands of different nature in one coordination sphere of rhodium was suggested.

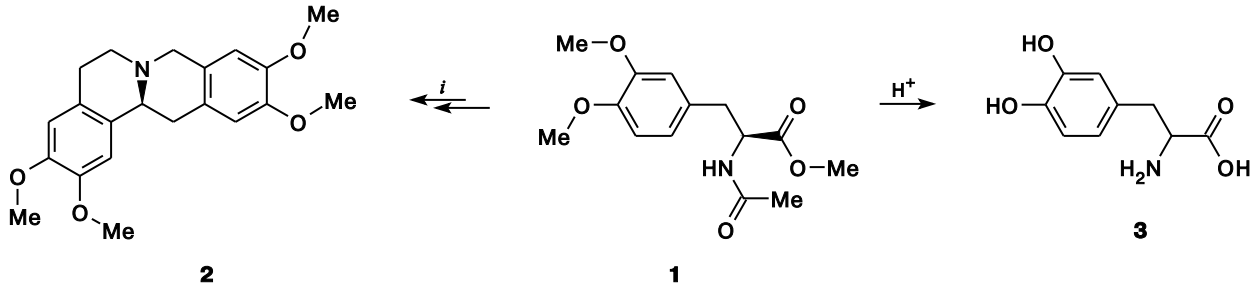
Key words: amidophosphites, hydrogenation, rhodium, methyl (*Z*)-2-acetamido-3-(3,4-dimethoxyphenyl)acrylate.

Optically active unnatural amino acids are valuable objects for the use in medicinal chemistry, as well as intermediates for the synthesis of a whole series of biologically active compounds.[1—6] Reactions of asymmetric metal-complex hydrogenation is a convenient approach to the preparation of chiral amino acid derivatives, which is characterized by low loading of catalysts and using hydrogen as the least expensive reducing agent.[7] Further treatment of the obtained products containing protecting groups, *viz.*, hydrolysis, leads to the target chiral unnatural amino acids.[1,7—11] Interesting objects also are methoxy-substituted phenylalanines used as key intermediates in the synthesis of proteinase inhibitors, that opens access to the new agents for cancer therapy.[12] In addition, (*S*)-3,4-dimethoxyphenylalanine derivative **1** found its application in the synthesis of berberine alkaloid, *viz.*, (*S*)-xylopinine (**2**),[13] it can be also used for the preparation of antiparkinsonian drug L-DOPA (**3**, Scheme 1).[8,11,14]

The most efficient ligands used nowadays in asymmetric hydrogenation are bidentate phosphines.[15,16] Comparatively recent studies showed that the use of synthetically available phosphite-type ligands in asymmetric hydrogenation also allows one to reach high degree of conversion and enantioselectivity (>99% *ee*).[17,18] Monodentate ligand L^1 is of special interest because of simplicity of its synthesis, availability of starting components, and efficiency in hydrogenation (see Refs 19—22).

To develop efficient and inexpensive process for the asymmetric hydrogenation of methyl (*Z*)-2-acetamido-3-(3,4-dimethoxyphenyl)acrylate (**4**) and synthesis of (*S*)-3,4-dimethoxyphenylalanine derivative **1**, we have

Scheme 1



2 **1** **3**

i. Four steps.

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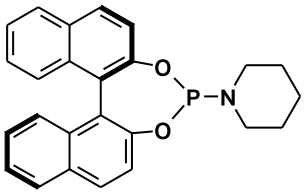
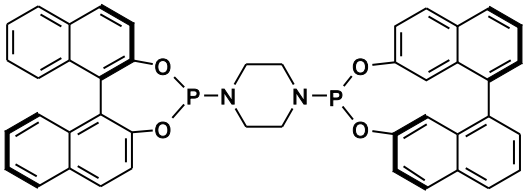


L^1



L^2

studied catalytic properties of ligand L^1 and its diamidophosphite analog L^2.

Results and Discussion

For obtaining methyl (*Z*)-2-acetamido-3-(3,4-dimethoxyphenyl)acrylate (**4**) (Scheme 2), we developed an express procedure, which includes reflux of azlactone **5** (see Ref. 8) in methanol. In this case, addition of metallic sodium in catalytic amount, which forms an active methylate, leads to the instantaneous dissolution of substrate **5** and further spontaneous precipitation of the reaction product **4**. Subsequent purification leads to the target enamide **4** in 90% yield.

An initial study of the catalytic system, obtained from $[Rh(COD)_2]BF_4$ (COD is the 1,5-cyclooctadiene) and amidophosphite ligand L^1, in the hydrogenation of methyl (*Z*)-2-acetamido-3-(3,4-dimethoxyphenyl)acrylate (**4**) was performed in a number of organic solvents (Table 1) at 50 °C because of poor solubility of the starting enamide **4** at room temperature. When the pressure of H_2 was 25 atm, it was found that in the presence of THF both conversion and enantioselectivity were rather low (see Table 1, entry *1*). Ethyl acetate and acetone lead to the higher conversion within 2 h, with the enantiomeric excess values being 60 and 68% *ee*, respectively. The use of CH_2Cl_2 as the solvent allowed us to reach 99.5% *ee* at 50% conversion within 2 h. The elevation of temperature from 50 to 70 °C promotes an increase in the rate of the process, with a small loss in enantioselectivity (see Table 1, entries *4* and *5*). An increase in the pressure of H_2 to 50 atm allowed us to quantitatively obtain the product within 140 min and with 99.3% *ee* at 50 °C.

To reach the optimum activity of the catalyst, we synthesized a cationic rhodium complex **6** (Scheme 3), which contains amidophosphite ligand L^1 and triphenylphosphine in the rhodium coordination sphere. The $^{31}P\{H\}$ NMR spectrum of compound **6** exhibits the corresponding spin-spin coupling constants $J_{PPh_3,L^1} = 33.5$, $J_{RhP,L^1} = 243.0$, $J_{RhP,PPh_3} = 145.8$ Hz and chemical shifts δ 137.0 and 30.5 corresponding to the amidophosphite and phosphine ligands. The elemental analysis data are in good agreement with the structure suggested. The use of Rh "mixed" complexes with one chiral and another achiral ligand in asymmetric hydrogenation was demonstrated in a number of works, nevertheless all these complexes were formed *in situ* starting from $[Rh(COD)_2]BF_4$ and the corresponding ligands.[23–26] In such a method of preparation, formation of both heterocombination $[(COD)RhL^1L^2]BF_4$ and two variants of homocombination ($[(COD)RhL^1L^1]BF_4$ and $[(COD)RhL^2L^2]BF_4$) is possible, with the homocombination from achiral ligand exclusively leading to the racemic product of the asymmetric reaction.[23] Our approach implies formation of only heterocomplex containing two different ligands. The study of activity of complex **6** in hydrogenation of substrate **4** showed that in the presence of complex **6**, the reaction rate is higher (see Table 1, entries *7—11*) than in the presence of the catalytic system containing two amidophosphite ligands (see Table 1, entries *1—6*), however, lower enantioselectivity values were observed when the "mixed" complex **6** was used. Complex **6** turned out to be rather sensitive to the reaction conditions. For instance, when hydrogenation was carried out in acetone at 25 atm of H_2 the product was formed with enantiomeric excess 66% *ee*. An increase in the pressure of H_2 to 50 atm leads to

Scheme 2

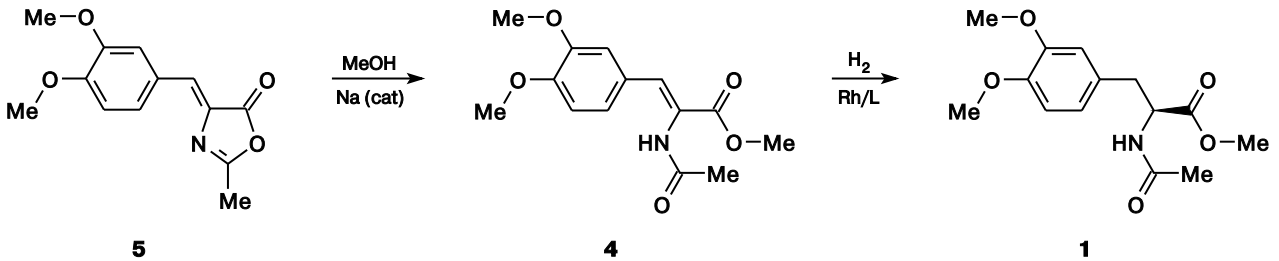


Table 1. Hydrogenation of methyl (*Z*)-2-acetamido-3-(3,4-dimethoxyphenyl)acrylate (**4**)

Entry	Catalyst	Solvent	P_{H_2}/atm	*T*/°C	*t*/min	Conversion (%)	*ee* (%)*
1	$[Rh(COD)_2]BF_4/2L^1$	THF	25	50	120	18	11
2	$[Rh(COD)_2]BF_4/2L^1$	EtOAc	25	50	120	70	60
3	$[Rh(COD)_2]BF_4/2L^1$	Acetone	25	50	120	100	68
4	$[Rh(COD)_2]BF_4/2L^1$	CH_2Cl_2	25	50	120	50	99.5
5	$[Rh(COD)_2]BF_4/2L^1$	CH_2Cl_2	25	70	120	78	98.5
6	$[Rh(COD)_2]BF_4/2L^1$	CH_2Cl_2	50	50	140	100	99.3
7	**6**	EtOAc	25	50	60	98	40
8	**6**	Acetone	25	50	60	100	66
9	**6**	Acetone	50	50	50	100	47
10	**6**	CH_2Cl_2	25	50	60	80	50
11	**6**	CH_2Cl_2	50	50	50	100	65
12	$[Rh(COD)_2]BF_4/L^2$	CH_2Cl_2	25	50	120	80	98
13	$[Rh(COD)_2]BF_4/L^2$	CH_2Cl_2	50	50	130	100	98.5

* (*S*)-Configuration in all the cases.

a decrease in enantioselectivity (see Table 1, entries *8* and *9*), with other reaction conditions remaining constant. Conversely, in CH_2Cl_2 an increase in the pressure of H_2 leads to the increase in the rate of the process, with enantioselectivity being also increased (see Table 1, entries *10* and *11*).

Scheme 3

6

We also studied catalytic properties of diamidophosphite ligand L^2 in CH_2Cl_2. An increase in the pressure of hydrogen from 25 to 50 atm favors both the hydrogenation rate of **4** and enantiomeric excess values for the reaction product **1** (see Table 1, entries *12* and *13*). Since the structure of ligands L^1 and L^2 are similar, the enantiomeric excess values are also similar under the same reaction conditions (Table 1, entries *4*, *6* and *12*, *13*). However, the hydrogenation rate on diamidophosphite ligand L^2 is somewhat higher.

In conclusion, we have offered a convenient express procedure for the preparation of methyl (*Z*)-2-acetamido-3-(3,4-dimethoxyphenyl)acrylate (**4**). Using synthetically available diamidophosphite ligands, a quantitative conversion and high enantioselectivity (to 99.5% *ee*) were reached in the preparation of the compound-precursor of valuable biologically active compounds. The known phosphine, phosphonite, and amidophosphite ligands used in this reaction are available by multi-step synthesis.[8,27–30] We have also for the first time developed an approach to the selective formation of cationic complexes containing two ligands of different nature in one coordination sphere of rhodium. The studies of "mixed" complex obtained on the activity in hydrogenation of methyl (*Z*)-2-acetamido-3-(3,4-dimethoxyphenyl)acrylate (**4**) showed that this catalyst is able to significantly accelerate the reaction. Although, a very high enantioselectivity was not observed in the presence of this catalyst, the introduction of achiral ligands with increased steric requirements, as well as different electronic characteristics, can be promising for the development of optimum catalysts for asymmetric metal complex catalysis.

Experimental

^{31}P and ^1H NMR spectra (161.98, 400.13 MHz) were recorded on an Avance 400 spectrometer. Elemental analysis was performed in the Laboratory of Organic Microanalysis of A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences. Ligands (R_{ax})-2-(8-piperidin-1-yl)-(dinaphtho[2,1-*d*:1′,2′-*f*][1,3,2]dioxaphosphepane) (L^1) and (R_{ax})-bis[(dinaphtho[2,1-*d*:1′,2′-*f*][1,3,2]dioxaphosphepanyl)]-1,4-piperazine (L^2), as well as $[Rh(COD)_2]BF_4$, were synthesized according to the known procedures.[20,31,32]

Synthesis of methyl (*Z*)-2-acetamido-3-(3,4-dimethoxyphenyl)acrylate (4). Metallic sodium (30 mg) was added to a boiling solution of 4-(3,4-dimethoxybenzylidene)-2-methyl-4*H*-oxazol-5-one (**5**) (5 g) in methanol (70 mL), an immediate dissolution of azlactone **5** was observed. The solution was refluxed for 5—10 min resulting in spontaneous precipitation of the reaction product. The mixture obtained was cooled (–10 °C), the product was filtered off, washed with methanol (15 mL) and CH_2Cl_2 (10 mL). Further recrystallization from ethyl acetate leads to compound **4** as a white powder. The yield was 5.08 g (90%). Spectral characteristics of **4** agree with the literature data.[8]

Synthesis of [{1,2:5,6-η-(1,5-cyclooctadiene)}{(R_a)-2-(3-piperidin-1-yl)-(dinaphtho[2,1-*d*:1′,2′-*f*][1,3,2]dioxaphosphepane}triphenylphosphine]rhodium tetrafluoroborate (6). Ligand L^1 (78 mg, 0.2 mmol) in CH_2Cl_2 (2 mL) was added to a solution of [1,2:5,6-η-(1,5-cyclooctadiene)]triphenylphosphinechloro-

rhodium[33] (100 mg, 0.2 mmol) in CH_2Cl_2 (5 mL). The mixture was stirred for 3 min, followed by addition of $AgBF_4$ (38 mg, 0.2 mmol) in THF (4 mL). The solution was additionally stirred for 40 min, a precipitate of AgCl was filtered off, the solvent was evaporated *in vacuo*. The product was purified on silica gel (chloroform). The yield of compound **6** was 141 mg (75%), an orange powder m.p. 205—210 °C (with decomp.). Found (%): C, 63.91; H, 5.24; N, 1.34. $C_{51}H_{49}BF_4NO_2P_2Rh$. Calculated (%): C, 63.83; H, 5.15; N, 1.46.

Asymmetric hydrogenation of methyl (*Z*)-2-acetamido-3-(3,4-dimethoxyphenyl)acrylate (general procedure). The compound $[Rh(COD)_2]BF_4$ (2 mg, 0.005 mmol) and ligand (0.005 or 0.01 mmol) or complex **6** (0.005 mmol) were added to the corresponding solvent (6 mL). The solution was stirred for 5 min, followed by addition of methyl (*Z*)-2-acetamido-3-(3,4-dimethoxyphenyl)acrylate **4** (138 mg, 0.5 mmol). An autoclave was purged with argon, filled with hydrogen to the required pressure. The reactor was heated to the corresponding temperature (10 min), and the experiments were performed by stirring the reaction mixture. After the reaction was completed, the hydrogen was slowly released, the reaction mixture was concentrated. Conversion of **4** was measured using ^1H NMR. Optical yields were determined by HPLC on a Agilent HP-1100 chromatograph using Chiralcel OJ-H columns (UV 219 nm, hexane/isopropanol = 7/3, 1 mL min^{-1}) according to the recommendations in the work.[28] The retention times for enantiomers of methyl 2-acetamido-3-(3,4-dimethoxyphenyl)propionate (**1**) were 9.3 (*R*) and 13.5 min (*S*), for enamide **4**, 16.4 min.

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