Asymmetric Ir-catalyzed hydrogenation of 1,5-benzodiazepinones using mixtures of ligands

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The catalytic hydrogenation of benzodiazepinones using metal complexes with phosphite and phosphoramidite ligands was carried out for the first time. The mixed-ligand catalytic systems containing a chiral phosphoramidite or phosphite in combination with an achiral phosphine were shown to exhibit a higher enantioselectivity compared to catalysts containing homocombinations of chiral ligands.

Key words: asymmetric hydrogenation, iridium, phosphoramidite, ligand mixtures, 1,5-benzodiazepine-2-ones.

Tetrahydro-1*H*-benzodiazepinones are a new class of bioactive compounds exhibiting antiasthmatic, anticancer, and neuroprotective properties.[1—3] At the present time, the asymmetric synthesis of such compounds[4,5] attracts attention of researchers. That is because one of enantiomers, part of the racemic mixture, can potentially produce a negative effect.[6] In the literature, the preparation of tetrahydro-1*H*-benzodiazepinones is described but in two works which used the Hantzsch esters as a reducing agent and chiral phosphoramidite as catalysts, as well as hydrosilylation reactions using the substituted proline as a catalyst.[4,5] Despite a high enantioselectivity, these approaches require quite difficult procedure for isolation of target products from the reaction mixture, as well as fairly expensive reducing agents. One of the most interesting atom-efficient reactions affording tetrahydro-1*H*-benzodiazepinones is asymmetric hydrogenation with metal complexes. This is due to the cheapness of hydrogen, low catalyst loadings, and simplicity of the work up procedure. Up to date, there were no examples of the asymmetric hydrogenation of dihydro-1*H*-benzodiazepinones on metal complex catalysts. Phosphites and phoshopramidites are efficient and synthetically available groups of ligands for the asymmetric hydrogenation of heterocyclic compounds with metal complexes.[7]

The present work is the first example of the asymmetric hydrogenation of dihydro-1*H*-benzodiazepinones using phosphoramidite and phosphite ligands. A positive effect observed when a mixture of chiral phosphite ligands was used in combination with achiral phosphines is also reported.

Results and Discussion

The initial experiments on hydrogenation of benzodiazepinone **1a** (Scheme 1) were performed using catalysts obtained *in situ* from the dimeric iridium precursor $[Ir(COD)Cl]_2$ (COD is 1,5-cyclooctadiene) and the monodentate phosphoramidite PipPhos (**L1**) in several organic solvents at 25 °C at hydrogen pressure of 70 atm (Table 1, Runs *1—4*). The highest enantiomeric excess of the reaction product (51%) was reached when hydrogenation was performed in dichloromethane. When the solvent was ethyl acetate, methanol, or ethanol, the quantitative conversion was achieved with a reduced enantioselectivity.

Scheme 1

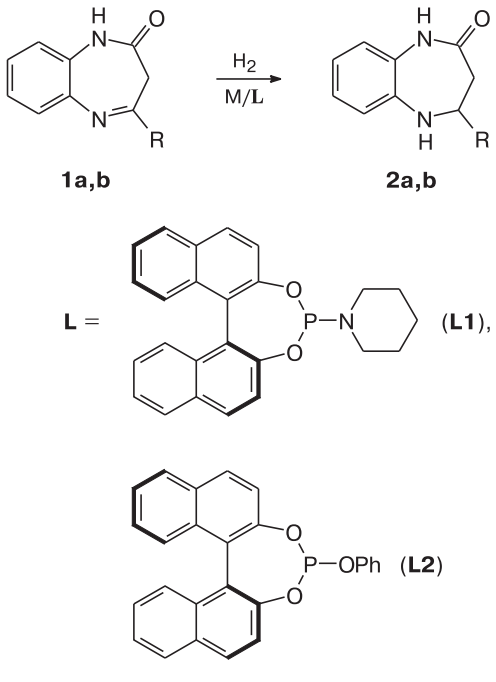

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Table 1. Data for the hydrogenation of 4-phenyl-1,3-dihydro-2*H*-1,5-benzodiazepine-2-one (**1a**)[a] with metal complexes

Run	Catalytic system	Medium	C^b (%)	ee^c (%)
1	$[Ir(COD)Cl]_2$/4**L1**	EtOAc	100	26(−)
2	$[Ir(COD)Cl]_2$/4**L1**	MeOH	100	44(−)
3	$[Ir(COD)Cl]_2$/4**L1**	EtOH	100	44(−)
4	$[Ir(COD)Cl]_2$/4**L1**	CH_2Cl_2	55	51(−)
5	$[Ir(COD)Cl]_2$/2**L1**, 2 PPh_3	CH_2Cl_2	35	38(−)
6	$[Ir(COD)Cl]_2$/2**L1**, 2 PCy_3	CH_2Cl_2	40	70(−)
7	$[Ir(COD)Cl]_2$/4**L2**	CH_2Cl_2	20	22(−)
8	$[Ir(COD)Cl]_2$/2**L2**, 2 PCy_3	CH_2Cl_2	35	0

[a] $T = 25$ °C, $P(H_2) = 70$ atm, $\tau = 24$ h, $[Ir(COD)Cl]_2$/**1a** = 1/200.
[b] C is conversion.
[c] The sign of specific rotation of the product is given within parentheses.

Table 2. Data for the metal complex hydrogenation of 4-methyl-1,3-dihydro-2*H*-1,5-benzodiazepine-2-one (**1b**)[a]

Run	Catalytic system	Medium	C^b (%)	ee^c (%)
1	$[Ir(COD)Cl]_2$/4**L1**	CH_2Cl_2	22	18(−)
2	$[Ir(COD)Cl]_2$/4**L1**	EtOH	100	28(−)
3	$[Ir(COD)Cl]_2$/2**L1**, 2 PPh_3	EtOH	100	73(−)
4	$[Ir(COD)Cl]_2$/2**L1**, 2 PCy_3	EtOH	100	5(−)
5	$[Ir(COD)Cl]_2$/2**L1**, 2 $P(Me)Ph_2$	EtOH	100	16(−)
6	$[Ir(COD)Cl]_2$/2**L2**, 2 PPh_3	EtOH	62	44(−)
7	$[Ir(COD)Cl]_2$/4**L2**	EtOH	100	0

[a] $T = 25$ °C, $P(H_2) = 70$ atm, $\tau = 24$ h, $[Ir(COD)Cl]_2$/**1b** = 1/200.
[b] C is conversion.
[c] The sign of specific rotation of the product is given within parentheses.

Upon hydrogenation of **1a**, an attempt was made to combine chiral phosphoramidite ligands with achiral phosphines. This approach is known for hydrogenation of heterocyclic compounds and, in some cases, allows one to considerably increase the enantioselectivity.[8,9] When **L1** was used in combination with triphenylphosphine, the conversion and the enantioselectivity were lower than those for hydrogenation with ligand **L1** only (see Table 1, cf. Runs *4* and *5*). Conversely, the replacement of triphenylphosphine with tricyclohexylphosphine (PCy_3) considerably increased the enantioselectivity to afford the target product in optical yield of 70% *ee*. This result can be explained by the formation of a sterically bulky complex with two ligands of different nature at one iridium atom.

Under these conditions (25 °C, 70 atm of H_2, CH_2Cl_2), we also tested the chiral phosphite **L2** in the asymmetric Ir-catalyzed hydrogenation of **1a**. However, for this ligand the conversion and the enantioselectivity were lower than those for phosphoramidite **L1** (see Table 1, *cf.* Runs *4* and *7*). The use of ligand **L2** in combination with tricyclohexylphosphine afforded the racemic product (see Table 1, Run *8*).

For the Ir-catalyzed hydrogenation of benzodiazepinone **1b** (see Scheme 1) involving ligand **L1** in dichloromethane, low conversions and enantioselectivity were obtained. The replacement of the solvent with ethanol allowed us to reach the quantitative hydrogenation and to increase its enantioselectivity compared to that observed in the reaction in dichloromethane (Table 2, *cf.* Runs *1* and *2*).

An attempt to use the chiral phosphoramidite ligand **L1** with achiral phosphines (triphenylphosphine or tricyclohexylphosphine) in hydrogenation of benzodiazepinone **1b** led to unexpected results. For example, when **L1** was used in combination with triphenylphosphine the highest enantiomeric excess of 73% was achieved; at the same time, the combination of **L1** with tricyclohexylphosphine showed the best result in hydrogenation of benzodiazepinone **1a** to afford the hydrogenation product **2b** with a low enantioselectivity (see Tables 2, Runs *3* and *4*). In hydrogenation of benzodiazepinone **1b**, we also tested a catalyst based on the combination of ligand **L1** with methyldiphenylphosphine ($P(Me)Ph_2$). In this case, the quantitative conversion was reached; however, the enantioselectivity was found to be lower than that using triphenylphosphine (see Table 2, *cf.* Runs *3* and *5*). The use of the combination of triphenylphosphine with the phosphite ligand **L2** was also found to be less efficient compared to the combination with phosphoramidite **L1** (see Table 2, Runs *3* and *6*). It is worthy of note that the use of **L2** without triphenylphosphine resulted in the racemic product (see Table 2, Run *7*).

Thus, we showed for the first time the possibility of the asymmetric hydrogenation of 1,3-dihydro-2*H*-1,5-benzodiazepine-2-ones with metal complex using phosphite-type ligands. The catalyst obtained by the combination of chiral phosphoramidites with achiral phosphines serves to considerably increase the enantioselectivity of the catalytic process compared to the homoligand catalytic systems, which suggests a promising outlook of this approach.

Experimental

^1H NMR spectra were recorded on a Bruker Avance 400 instrument (400.13 MHz) relative to Me_4Si. Hydrogenation was performed on an installation (High pressure equipment) equipped with a 10-mL stainless steel pressure vessel. The optical yields were determined by chiral HPLC on an Agilent HP-1100 chromatograph using Kromasil 3-AmyCoat columns (UV 219 nm, hexane: isopropanol = 90 : 10, 1 mL min^{-1}). The retention times for the enantiomers of 4-phenyl-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepine-2-one (−)-**2a** and (+)-**2a**

were 17.4 and 19.3 min, respectively, and the retention time of 4-phenyl-1,3-dihydro-2*H*-1,5-benzodiazepine-2-one (**1a**) was 9.1 min. The retention times for the enantiomers of 4-methyl-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepinone-2-one (–)-**2b** and (+)-**2b** were 16.5 and 23.4 min, respectively, and the retention time of 4-methyl-1,3-dihydro-2*H*-1,5-benzodiazepine-2-one (**1b**) was 6.6 min. Conversions of **1a** and **1b** were determined by ^{1}H NMR spectroscopy; the spectral characteristics of products **2a** and **2b** correspond to the earlier published data.[10] 4-Phenyl-1,3-dihydro-2*H*-1,5-benzodiazepine-2-one (**1a**),[11] (S_a)-2-(piperidin-1-yl)-dinaphtho[2,1-*d*:1′,2′-*f*][1,3,2]dioxaphosphepine (**L1**),[12] (S_a)-2-(phenoxy)-dinaphtho[2,1-*d*:1′,2′-*f*][1,3,2]dioxaphosphepine (**L2**),[13] and $[Ir(COD)Cl]_2$[14] were prepared according to the earlier published procedures. The spectral characteristics of compound **1a** correspond to the literature data.[15]

Synthesis of 4-methyl-1,3-dihydro-2*H*-1,5-benzodiazepine-2-one (1b). To a solution of acetyl chloride (0.1 mol, 7.8 g) in diethyl ether (100 mL) cooled on an ice bath, triethylamine (16.7 mL, 0.12 mol) was added dropwise in argon atmosphere for 30 min and the resulting mixture was stirred for 1 h. To the formed diketone which is instable at room temperature and toxic, a solution of 1,2-diaminobenzene (0.04 mol, 4.3 g) in acetonitrile (50 mL) was added. The mixture was stirred on an ice bath for 1 h and kept at room temperature for 8 h. Water (30 mL) was added to the reaction mixture and the product was extracted with ethyl acetate (3×25 mL). The organic phase was dried with sodium sulfate and the solvent was removed *in vacuo*. The product was purified by recrystallization from ethyl acetate. The yield was 38%. The spectral characteristics of **1b** correspond to the literature data.[16]

Asymmetric hydrogenation (general procedure). The dimer $[Ir(COD)Cl]_2$ (2.5 mg, 0.0037 mmol) and chiral ligand (0.0148 mmol) or a mixture of chiral (0.0074 mmol) and achiral (0.0074 mmol) ligands (see Tables 1 and 2) wer e dissolved in CH_2Cl_2 (0.4 mL) and the resulting mixture was stirred on a magnetic stirrer in a 10-mL pressure vessel for 5 min. The solvent was removed *in vacuo*. 4-Phenyl-1,3-dihydro-2*H*-1,5-benzodiazepine-2-one (**1a**) or 4-methyl-1,3-dihydro-2H-1,5-benzodiazepine-2-one (**1b**) (0.74 mmol) were added to the resulting catalysts; the pressure vessel was filled with hydrogen (70 atm) and the experiments were performed with stirring on a magnetic stirrer. After release of hydrogen, the reaction mixture was diluted with CH_2Cl_2 (2 mL) and purified from the catalyst through a thin silica gel layer and the solvents were removed *in vacuo*.

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