Iridium-Catalyzed Enantioselective Hydrogenation of Imines with Xylose Diphosphite and Diphosphinite Ligands

Ester Guiu, Bianca Muñoz, Sergio Castillón,* Carmen Claver*

Departament de Química Física i Inorgànica and Departament de Química Analítica i Química Orgánica, Universitat Rovira i Virgili, Pl. Imperial Tàrraco 1, 43005 Tarragona, Spain
Fax: (+34)-977-559-563, e-mail: castillon@quimica.urv.es, claver@quimica.urv.es

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Abstract: Iridium complexes incorporating xylose diphosphinite **1** and diphosphite **2**, **3** ligands as source of chirality are active catalysts for the hydrogenation of imines providing moderate ee. The enantioselectivity depends on the fine tuning of the structural parameters of the ligand and on the effect of additives.

Keywords: asymmetric catalysis; diphosphinite; diphosphite, hydrogenation, imines, iridium, P-ligands

The synthesis of enantiomerically enriched amines from prochiral compounds is of considerable industrial interest. The development of efficient catalysts for the enantioselective conversion of prochiral imines to the corresponding chiral amines is a major target of research.[1] Although the enantioselective hydrogenation of olefins and ketones has been successfully achieved with several catalytic systems using phosphorus ligands, high enantioselectivities have been obtained in only a few cases in the hydrogenation of imines.[2]

Among some notable achievements in this field, Spindler reported an iridium catalyst prepared *in situ* with Xyliphos ligand and applied it to the industrial production of (*S*)-metolachlor.[3] More recently, Pfaltz investigated the application of cationic Ir(I) complexes with diphenylphosphinooxazolines in the reduction of imines. This catalyst, which provides enantioselectivies of 89% in acyclic substrates, represents one of the most successful examples of cationic precursors used in the asymmetric hydrogenation of imines.[4]

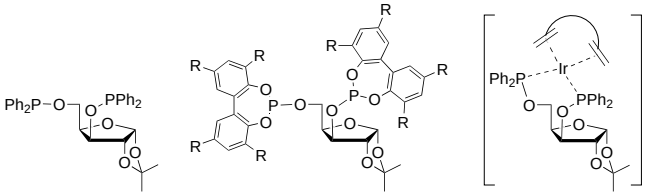
Osborn developed Ir(III) complexes of the type $[Ir_2(P\text{-}P)_2I_4H_2]$. These systems showed good activities in the reduction of cyclic imines but the enantioselectivities were generally moderate.[5] A highly enantioselective hydrogenation of acyclic imines catalyzed by Ir-ferrocene-binaphane complexes has been reported by Zhang.[6] Bianchini explored the use of an *ortho*-metallated dihydride-iridium complex in the reduction of quinoxalines with ee up to 90%.[7] Buchwald and coworkers have developed a chiral *ansa*-titanocene catalyst with the 1,1′-binaphthyl-2,2′-diolate ligand that was highly effective in the reduction of cyclic imines.[8] Finally, Chiro-Tech has patented a ruthenium catalyst [Ru(DUPHOS)(chiral diamine)Cl_2] that achieves enantioselectivities up to 91% in the hydrogenation of *N*-(phenylethylidene)aniline.[9]

Iridium-diphosphines are the most effective and widely used systems in the hydrogenation of imines, but all these systems generally have a very limited substrate scope.

It is interesting that, apart from diphosphines, other chelating phosphorus ligands have scarcely been used in the reduction of imines. There are only a few examples in the literature in which diphosphinites have been reported as ligands in both rhodium and iridium systems with moderate to good enantioselectivities.[10,11] An example of the use of an amidophosphine-phosphinite ligand is reported for the hydrogenation of cyclic iminium salts.[12] However, as far as we know, no diphosphite ligands are reported that provide enantioselectivity in the asymmetric hydrogenation of imines.

The potential of chiral diphosphinite and diphosphite ligands in hydrogenation has been demonstrated in recent reports.[13,14] In the last years we have successfully used different types of phosphorus ligands with a xylofuranoside backbone in homogeneous catalysis.[15]

Because of these results, we thought it interesting to apply the xylose-diphosphinite (**1**)[16] and -diphosphites (**2**, **3**)[17] as ligands to the hydrogenation of imines. In this study we report the preliminary results in the hydrogenation of *N*-(phenylethylidene)benzylamine (**5**) and *N*-(phenylethylidene)aniline (**7**).



1 **2** R = H, **3** R = *t*-Bu **4**

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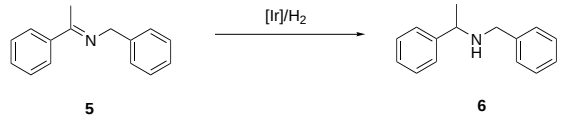

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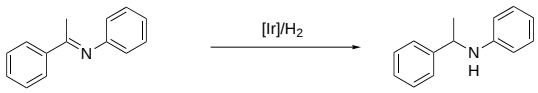
Scheme 1.



7 8

Scheme 2.

We first explored the use of the iridium catalytic precursors $[Ir(cod)(L\text{-}L)]BF_4$ (L-L = **1**–**3**) in the hydrogenation of imine **5** (Scheme 1). These catalytic systems were active at 50 bar of hydrogen and 25 °C and provided complete hydrogenation into the amine **6** in 16h.

The iridium system containing ligand **2** did not provide enantioselectivity in all the conditions, even when several solvents and pressures were tested. Only with ligands **1** and **3** did we obtain moderate ee (46 and 21%, respectively).

However, we found that in the hydrogenation of this substrate, the ee values obtained were not reproducible, even when the conditions were strictly maintained. It has been previously reported that ees obtained in the asymmetric hydrogenation of *N*-(phenylethylidene)-benzylamine are poorly reproducible.[10]

A different behavior was observed when we studied the hydrogenation of imine **7** to produce amine **8** (Scheme 2). Table 1 collects the results of the hydrogenation using the diphosphinite ligand **1**.

We studied the hydrogenation of **7** at different pressures and temperatures using the complex [Ir(cod)**1**]BF_4 (**4**) as catalyst precursor. The best enantioselectivities were obtained at low pressures (Table 1, entries 1–3), when an enantioselectivity up to 57% was achieved. Curiously, higher substrate/catalyst ratio and lower temperature decrease the enantioselectivity (Table 1, entries 4, 5 and 6). Several reports have shown that an additive is necessary for improving catalytic activity and enantioselectivity. Among the most widely used additives are halides and iodides.[10,18] However, when Bu_4NI was used as additive the enantioselectivity fell sharply (Table 1, entry 7).

Concerning the diphosphite ligands **2**, **3**, the catalytic system $[Ir(cod)_2]BF_4$/**2** was moderately active in the hydrogenation of imine **7** (Table 2, entry 1). It selectively provided the amine **8** but did not achieve enantioselectivity.

The use of additives, such as Bu_4NI and iodine, improved conversion but did not modify the ee (Table 2, entries 2, 3). The catalytic system $[Ir(cod)_2]BF_4$/**3** was more active but initially did not provide ee. However, when Bu_4NI was used as additive the ee increased to 46% (entry 5). This confirms the importance of additives in the asymmetric hydrogenation of imines and shows for the first time that phosphite ligands can also provide ee in this process. Iodine also improved the enantiomeric excess, but not as much as Bu_4NI (entry 6). Phthalimide and benzylamine have been also used as additives, but these promoted the deactivation of the catalytic system (entries 7, 8).

The presence of bulky *tert*-butyl groups in the *ortho*-positions of the biphenyl moiety has an extremely positive effect on enantioselectivity (Table 2, entries 2, 5), as was previously found in the hydrogenation of dehydroamino acids derivatives.[15c]

In conclusion, diphosphite ligands have provided for the first time moderate enantioselectivity in the asymmetric hydrogenation of imines. Diphosphite ligands derived from sugars appear to be promising ligands in this process. The enantioselectivity depends on the fine tuning of the structural parameters of ligand as well as on the effect of additives.

Table 1. Hydrogenation of imine **7** using complex **4** as catalyst.[a]

Entry	P [bar]	T [°C]	Additive	Conversion [%]	ee [%]
1	10	25	–	83	57 (*S*)
2	25	25	–	95	56 (*S*)
3	50	25	–	92	38 (*S*)
4[b]	50	25	–	20	22 (*S*)
5	85	25	–	98	30 (*S*)
6	25	0	–	85	20 (*S*)
7[c]	25	0	Bu_4NI	96	15 (*R*)

[a] [cat] = 1%; time 18 h; solvent = CH_2Cl_2.
[b] [cat] = 0.1%.
[c] Time 5 h.

Table 2. Hydrogenation of imine **7** using [Ir]/**2** and **3** as catalytic systems.[a]

Entry	Ligand	Additive[b]	Conversion [%]	ee [%]
1	2	–	40	0
2	2	Bu_4NI	78	0
3	2	I_2	100	0
4	3	–	100	5
5	3	Bu_4NI	100	46
6	3	I_2	100	31
7	3	Phthalimide	47	9
8	3	$BnNH_2$	7.2	7.2

[a] [[Ir(cod)]BF_4] = 1%; ratio [Ir]/L = 1; pressure = 70 bar; temperature 25 °C; time = 16 h; solvent = CH_2Cl_2.
[b] [Additive] = 4%.

Experimental Section

Synthesis of $[Ir(COD)(1)]BF_4$ (4)

To a chilled ($-80\,^{\circ}C$) solution of $[Ir(COD)_2]BF_4$ (150 mg, 0.3 mmol) in dry and deoxygenated dichloromethane (4 mL) was added dropwise a solution of **1** (250 mg, 0.4 mmol) in dry and deoxygenated dichloromethane (5 mL). The mixture was allowed to warm to $0\,^{\circ}C$ and stirred for 15 min. At that time diethyl ether (30 ml) was added to precipitate the desired product as a pale purple solid; yield: 322 mg (76%); Anal. calcd.: C 52.65, H 5.85%; found: C 52.80; H 5.69; ^{31}P NMR (161.9 MHz, $CDCl_3$): $\delta = 114.1$ (d, $^2J_{P,P} = 27.4$ Hz), 110.2 (d, $^2J_{P,P} = 27.5$ Hz).

General Procedure for the Ir-Catalyzed Hydrogenation of Imines

A flask (150 mL) with a magnetic stirring bar was charged under a nitrogen atmosphere with a solution of $[Ir(COD)\mathbf{1}]BF_4$ (0.022 mmol, 28.09 mg) and *N*-(phenylethylidene)aniline (**7**; 2 mmol, 0.39 g) in 10 mL of anhydrous and deoxygenated CH_2Cl_2 and placed in a steel autoclave. The reaction mixture was stirred overnight at room temperature under 25 bar of H_2 pressure. Gas chromatographic analyses were performed using a Hewlett-Packard 5890A. The conversion was measured with an Ultra-2 (5% diphenylsilicone/95% dimethylsilicone) column (25 m $\times$ 0.2 mm Φ). The enantiomeric excess of *N*-phenyl-1-phenylethylamine (**8**) was determined by chiral gas chromatography after derivatization into the acetamide compound. Chiral column FS-Cyclodex b-I/P, 50 m $\times$ 0.25 mm.

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