

## Highly Enantioselective Imine Hydrogenation catalyzed by Ruthenium phosphane-phosphite diamine complexes

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*Dedicated to Prof. José Gimeno on the occasion of his 65th birthday*

The exceedingly high performance of RuCl<sub>2</sub>(diphosphane)-(diamine) complexes in the asymmetric hydrogenation of ketones<sup>[1]</sup> has focused a great interest on the reactivity of Ru(II) complexes based on phosphorus and amino ligands. Thus, a wide diversity of structurally related chiral complexes (e. g. RuX<sub>2</sub>(P-P)(N-N), RuX<sub>2</sub>(P)<sub>2</sub>(N-N), RuX<sub>2</sub>(P-N)<sub>2</sub>; X = anionic ligand) has been described.<sup>[2]</sup> Most notably, these compounds have displayed a rich reactivity, providing active catalysts for the hydrogenation of different types of substrates.<sup>[3-5]</sup> In addition, applications of these complexes in catalytic transfer hydrogenation,<sup>[6]</sup> cycloaddition,<sup>[7]</sup> conjugate addition,<sup>[8]</sup> or hydrocyanation reactions,<sup>[9]</sup> have also been reported.

Due to the industrial importance of chiral amines, a highly interesting application of the aforementioned Ru complexes is the asymmetric catalytic hydrogenation of imines.<sup>[10]</sup> As best

enantioselectivities for these substrates are normally achieved with Ir catalysts,<sup>[11]</sup> a general goal in this area is the development of catalysts based on less costly metals.<sup>[12]</sup> At this regard, the group of Morris has reported that several Ru hydrides give active catalysts for imine hydrogenation reactions, while BINAP complexes with DPEN and DACH diamines gave moderate enantioselectivities.<sup>[5]</sup> Moreover, Cobley and coworkers, following a systematic optimization of both the diamine and diphosphane ligands, found a highly enantioselective catalyst, based on Et-DuPHOS and DACH, for the hydrogenation of *N*-(1-phenylethylidene)aniline.<sup>[13]</sup> Very recently, Ohkuma et al have described a highly efficient catalyst based on Xyl-skewphos and DPEN ligands for the hydrogenation of a wide range of imines.<sup>[14]</sup>

A remarkable feature of  $\text{RuX}_2(\text{P-P})(\text{N-N})$  complexes is the presence of four tunable coordinating P and N groups, offering rather unlimited possibilities for catalyst optimization. Among the possible combinations, particularly appealing for practical reasons are those based on only one chiral ligand.<sup>[15]</sup> Moreover, most of the catalytic applications described with these Ru complexes have been performed with  $C_2$ -symmetric diphosphane and diamine ligands. However, the use of unsymmetric bidentate N-N' ligands (Figure 1) have produced remarkable achievements in ketone hydrogenation.<sup>[16]</sup> In contrast, the application of phosphorus ligands with two different P coordinating fragments (P-P') is practically unexplored, limited to the best of our knowledge, to the diastereoselective formation of a highly active transfer hydrogenation catalyst based on a Josiphos diphosphane, reported by Baratta et al.<sup>[6c]</sup> In this contribution we deep on the high potential of Ru derivatives based on P-P' ligands. Thus, a practical highly enantioselective catalyst for the catalytic hydrogenation of *N*-aryl imines, based on an achiral phosphane-phosphite and DPEN is described.

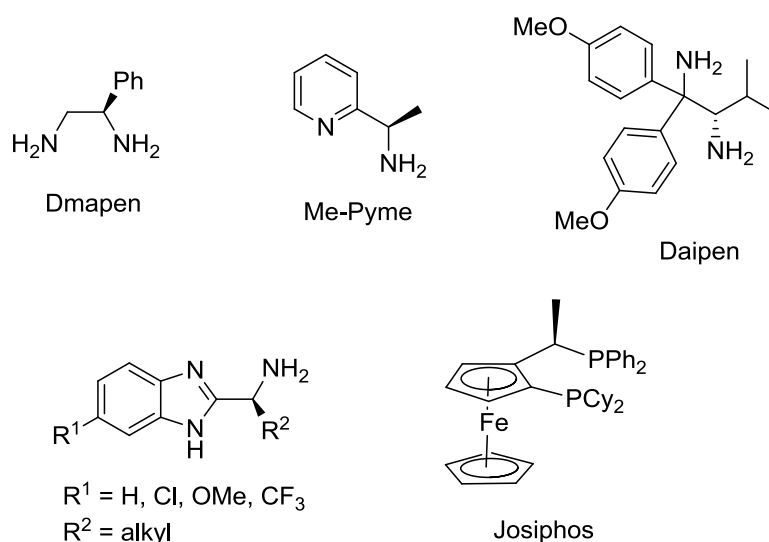
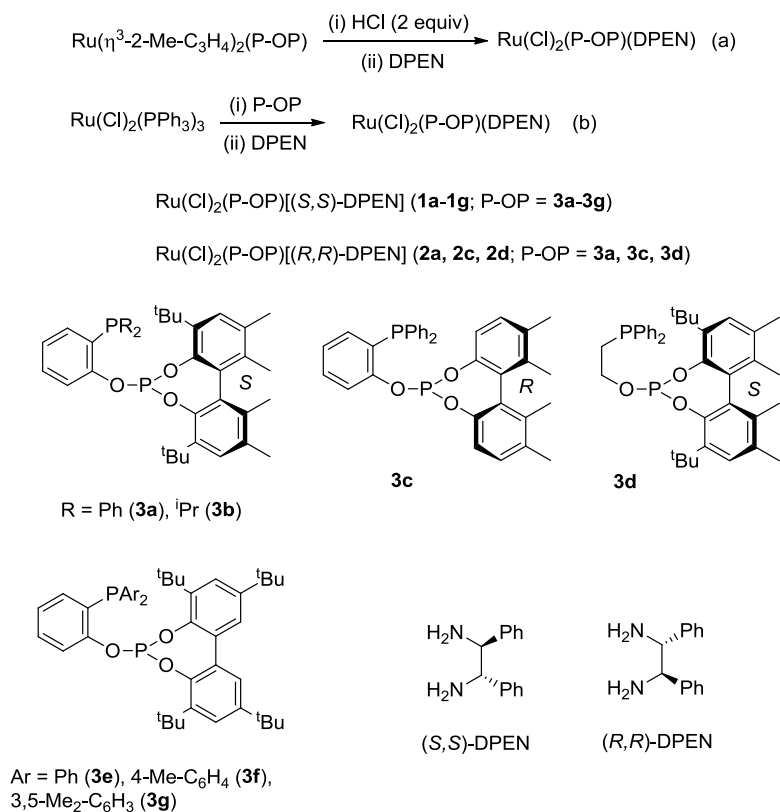


Figure 1. Some  $C_1$  symmetric N-N' and P-P' ligands.

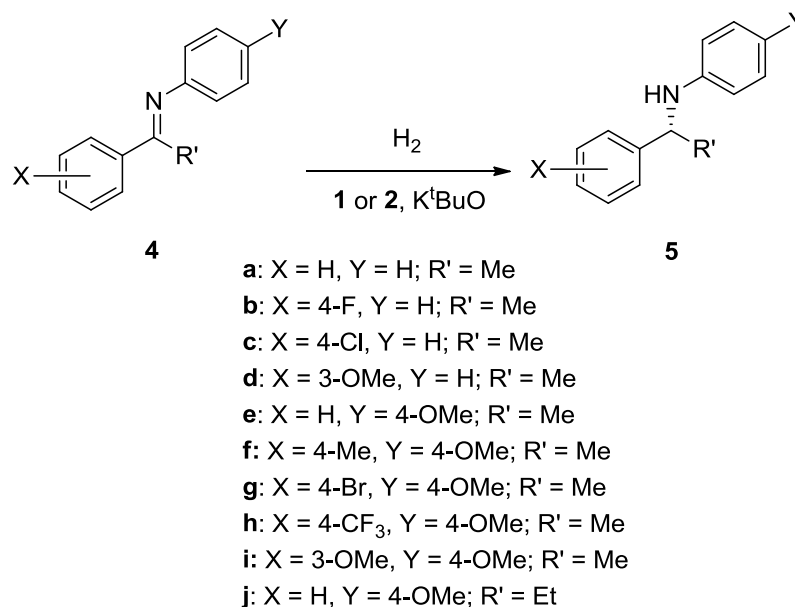
In recent years we have studied the application of a family of chiral phosphane-phosphites (P-OP) in diverse Rh, Ru and Ir asymmetric catalytic hydrogenations.<sup>[17]</sup> The highly modular structure of these ligands, the rich catalytic reactivity of  $\text{RuCl}_2(\text{diphosphane})(\text{N-N})$  complexes and the lack in the literature of phosphane-phosphite analogues, committed us to investigate the preparation of some derivatives bearing P-OP ligands. Initially, reaction of  $\text{Ru}(2\text{-Me-C}_3\text{H}_4)_2(\text{P-OP})$ <sup>[17f]</sup> with two equivalents of HCl and one equivalent of (*S,S*)-DPEN yielded complexes **1a-1g**. Alternatively, complexes **2a**, **2c** and **2d** were prepared using (*R,R*)-DPEN (Scheme 1a). On the other hand, treatment of  $\text{Ru}(\text{Cl})_2(\text{PPh}_3)_3$  with one equivalent of ligand **3**, followed by a stoichiometric amount of DPEN, provides an easy access to the desired compounds (Scheme 1b). Depending on the nature of P-OP and DPEN ligands these reactions produced compounds **1** and **2** either as a single diastereomer, or as mixtures containing two or three isomers, from which the major one was purified by column chromatography. In addition, the major isomer can display either *cis*- or *trans*-dichloride coordination depending on the combination of the chelating ligands (see below).



Scheme 1. Preparation of complexes **1** and **2**.

We have next screened the performance of complexes **1** and **2** in the enantioselective hydrogenation of *N*-(1-phenylethylidene)aniline **4a** (Scheme 2, Table 1). As a first approach, similar reaction conditions to those reported by Cobley were used (i. e. S/C = 100, <sup>i</sup>PrOH as solvent, 20 bar H<sub>2</sub>, [**4a**]/[K<sup>t</sup>BuO] = 1, 60 °C).<sup>[13]</sup> Under these conditions compounds **1a** and **1b** gave moderate conversions, while the diphenyl catalyst provided a significantly better enantioselectivity (entries 1, 2, Table 1). Moreover, precatalysts with a smaller phosphite fragment **1c** (entry 3) and an ethane backbone **1d** (entry 4) were also examined. None of them increased the enantioselectivity provided by **1a**, although the ethane bridged catalyst, probably due to a more flexible backbone, produced a higher conversion. To examine matching effects between diamine and P-OP ligands diastereomeric complex **2a** was also tested. This compound produced a similar conversion and a higher enantioselectivity (90 % ee, entry 8) than **1a**. These

results indicate that the chiral induction is very predominantly caused by the diamine ligand and that the stereogenic axis of the phosphite has a secondary role. Following this reasoning we next examined complex **1e** bearing a conformationally flexible phosphite fragment. We were pleased to observe that this compound produced the same enantioselectivity than **2a** (90 % ee, entry 5) but with better conversion. Interestingly, these results indicate that an important variable is phosphite flexibility, which enables a higher catalyst reactivity, while the use of a more rigid phosphite fragment with a stereogenic axis retards the reaction and does not improve enantioselectivity. In addition, these results enable a further optimization of the catalyst using other achiral P-OP ligands differing on the phosphane group. Then, complexes **1f** and **1g** bearing *p*-tolyl and xylyl phosphane substituents were examined. While the latter produced moderate levels of conversion and enantioselectivity (entry 7), catalyst precursor **1f** provided a higher enantioselectivity than **1a**, with an important improvement on conversion (entry 6).



Scheme 2. Catalytic Hydrogenation of *N*-aryl imines.

Table 1. Hydrogenation of **4a** with complexes **1**, **2**<sup>[a]</sup>

Entry	P-OP	N-N	Conv [%]	Ee [%]	Config
1	<b>3a</b>	( <i>S,S</i> )-DPEN	39	80	<i>R</i>
2	<b>3b</b>		47	32	<i>R</i>
3	<b>3c</b>		55	58	<i>R</i>
4	<b>3d</b>		72	73	<i>R</i>
5	<b>3e</b>		67	90	<i>R</i>
6	<b>3f</b>		97	93	<i>R</i>
7	<b>3g</b>		78	72	<i>R</i>
8	<b>3a</b>	( <i>R,R</i> )-DPEN	39	90	<i>S</i>
9	<b>3c</b>		24	12	<i>S</i>
10	<b>3d</b>		70	54	<i>S</i>

[a] Reactions were carried out at 60 °C using 0.1 M solutions of substrate and K<sup>t</sup>BuO as base (B), S/C/B = 100/1/100, reaction time 72 h. Conversion was determined by <sup>1</sup>H NMR and enantiomeric excess by Chiral HPLC. Configuration was determined by comparison of sign of optical rotation with literature data (see supporting information).

Most remarkably, precatalyst **1f** showed a high reactivity in toluene, enough to complete reactions under very mild conditions at lower catalyst and base loadings (room temperature, 4 bar H<sub>2</sub>, S/C/B = 500/1/10). Under these conditions a 93 % ee in the hydrogenation of **4a** was reached (entry 1, Table 2). These results prompted us to investigate the scope of the present catalytic system. We were pleased to observe that diverse *N*-aryl imines **4** were hydrogenated with high levels of conversion and enantioselectivities under these reaction conditions (Scheme 2). In general, *N*-phenyl imines gave somewhat lower enantioselectivities (91-93 % ee, entries 1-4), than *N*-(*p*-anisyl) imines, which provided values from 93 to 96 % ee (entries 5, 6, 8, 10-12), in good accord with previous observations.<sup>[11g, 14]</sup> During this screening we have observed that substrates **4g** and **4h** gave uncompleted reactions under the latter reaction conditions. An

increase in the pressure to 10 bar of hydrogen produced amine **5g** with full conversion and a 95 % ee (entry 8). In the case of the trifluoromethyl substituted imine **4h**, reaction in <sup>1</sup>PrOH under 20 bar showed full conversion with a 93 % ee (entry 10). Finally, *N*-(*p*-methoxyphenyl)-1-phenylpropylamine **5j** was obtained with a 95 % ee and complete conversion by hydrogenation of the corresponding imine **4j** (entry 12).

Table 2. Hydrogenation of imines **4** with complex **1f**<sup>[a]</sup>

Entry	Substrate	H <sub>2</sub> [bar]	Conv [%]	Ee [%]	Config <sup>[b]</sup>
1	<b>4a</b>	4	> 99	93	<i>R</i>
2	<b>4b</b>	4	> 99	93	-
3	<b>4c</b>	4	> 99	91	<i>R</i>
4	<b>4d</b>	4	> 99	92	-
5	<b>4e</b>	4	> 99	95	<i>R</i>
6	<b>4f</b>	4	> 99	96	<i>R</i>
7	<b>4g</b>	4	73	89	<i>R</i>
8	<b>4g</b>	10	> 99	95	<i>R</i>
9	<b>4h</b>	4	26	81	<i>R</i>
10 <sup>[c]</sup>	<b>4h</b>	20	> 99	93	<i>R</i>
11	<b>4i</b>	4	> 99	96	-
12	<b>4j</b>	4	> 99	95	<i>R</i>

[a] Reactions were carried out at room temperature in toluene with K<sup>t</sup>BuO as base (B), S/C/B = 500/1/10, reaction time 24 h and [S] = 1.0 M, unless otherwise specified. Conversion was determined by <sup>1</sup>H NMR and enantiomeric excess by Chiral HPLC. [b] Configuration was determined by comparison of sign of optical rotation with literature data when available (see supporting information), otherwise the optical rotation sign is provided. [c] Reaction performed at 60 °C in <sup>1</sup>PrOH.

With the intention to gain additional information about the stereochemistry of Ru complexes, representative examples **2d** and **1e** were structurally characterized by X-ray crystallography.<sup>[18]</sup> Both compounds show a distorted octahedral structure and noteworthy

differ in the coordination positions of chloride ligands. Complex **2d** shows a *cis* arrangement with one of the chlorides *trans* to the phosphite group (Figure 2). In addition, this structure displays a significant *trans* influence of the phosphite group as the Ru-Cl(2) distance is appreciable longer than that Ru-Cl(1) (2.475 and 2.409 Å, respectively). In contrast, structure of compound **1e** shows two chlorides in two mutually *trans* positions (Figure 3). A remarkable feature of this compound is the existence in the crystal of two diastereomeric molecules differing in the conformation of the biphenyl fragment. The dissimilarity between the two structures is not restricted to the phosphite fragment, as the change in biaryl conformation is coupled with opposed conformations of the benzene backbone and the phosphane group. Thus, if the diamine backbone is ignored both structures are nearly enantiomeric each other. In solution, however, only one set of signals composed by two doublets centered at 146.1 and 38.7 ppm [ $J(\text{P,P}) = 73$  Hz], was observed by  $^{31}\text{P}\{^1\text{H}\}$  NMR at room temperature. Upon cooling, signals broadened and at -90 °C two species in a 2:1 ratio were observed. The major species appeared as two doublets centered at 149.5 and 37.3 ppm [ $J(\text{P,P}) = 71$  Hz], while the minor one is characterized by two doublets at 148.8 and 36.9 ppm [ $J(\text{P,P}) = 73$  Hz]. These observations are in accord with a fast exchange between the two diastereomers upon atropisomerization of the phosphite group at room temperature, as observed in rhodium derivatives bearing this phosphite fragment.<sup>[19]</sup> Therefore, the chiral diamine does not efficiently favour a phosphite biaryl conformation, as observed before in the case of complexes based on conformationally flexible diphosphanes.<sup>[20]</sup>



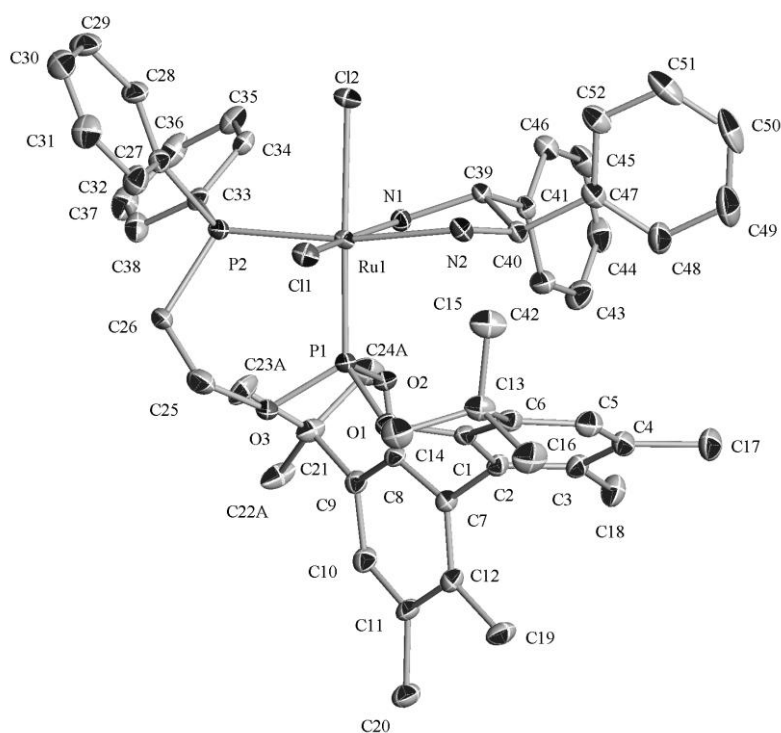


Figure 2. ORTEP view of complex **2d**.

The high enantioselectivity provided by **1e**, along with the lack of chiral control of the diamine in phosphite conformation constitute a remarkable aspect which deserves further comment. Assuming that the hydrogenation of *N*-aryl imines proceeds in an analogous manner to ketone hydrogenation,<sup>[21]</sup> several structures for the key dihydride with *cis* hydride and amino ligands are possible.<sup>[22]</sup> Namely, a *trans* dihydride **A** (Figure 4) and diastereomeric *cis* structures **B** and **C** differing in the relative positions of the P functionalities (only diastereomers corresponding to  $\Delta$  Ru configuration are shown). Among these structures, dihydride **B**, which is structurally similar to **2d**, places the more reactive hydride (according to the higher phosphite *trans* influence over that of the amino ligand) in a *trans* position to the phosphite group. This arrangement would minimize the influence of phosphite conformation on asymmetric induction, in good accord with experimental results. This proposal finds further support on the stereochemical model proposed by Ohkuma, based on a *cis* dihydride in which the apical hydride, *trans* to a phosphane ligand, is transferred to the *N*-aryl imine.<sup>[14]</sup> Moreover, the

stereochemical outcome provided by complexes **1** and **2** [i.e. catalysts based on (*S,S*)-DPEN give *R* amines] is analogous to that rationalized by the mentioned model.

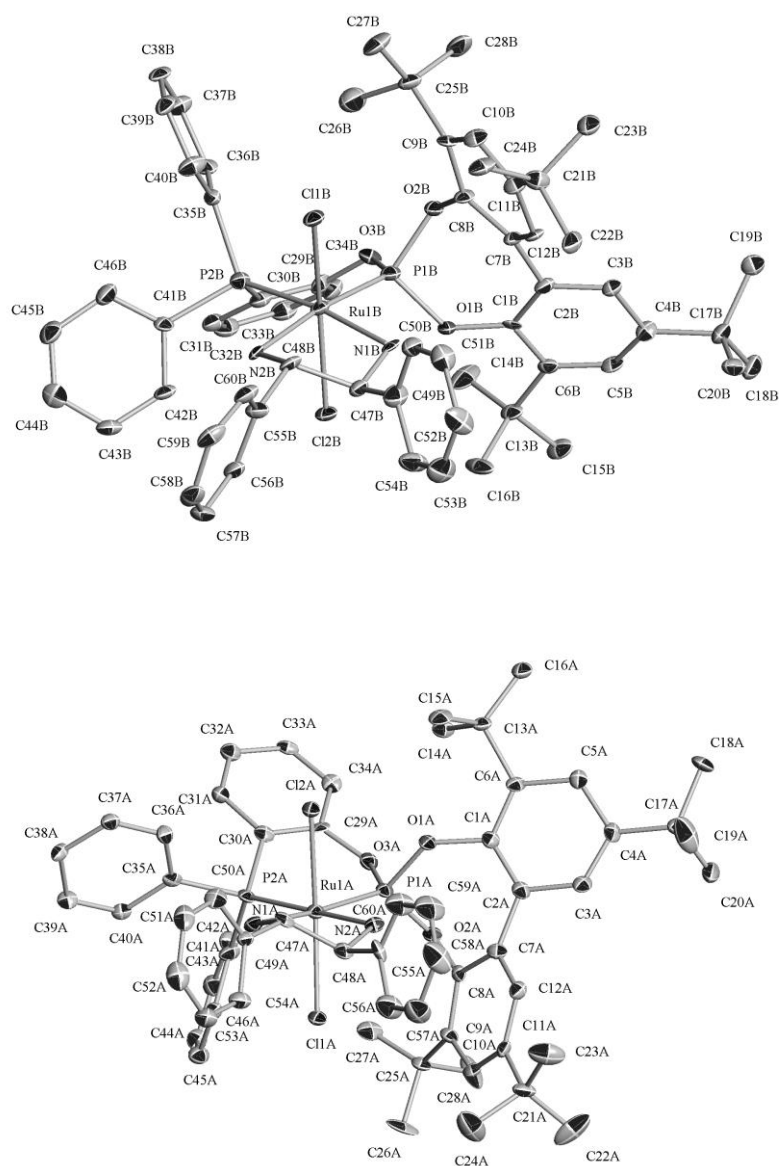


Figure 3. ORTEP views of  $S_a$  (top) and  $R_a$  (bottom) conformers of **1e**.

Therefore, a new catalytic system for the hydrogenation of imines, based on Ru complexes with phosphane-phosphite and diamine ligands has been described. Following a ligand screening, a practical catalyst which possesses a conformationally flexible phosphane-phosphite and DPEN has been found. This catalyst operates under very mild conditions and

provides up to 96 % ee in the hydrogenation of *N*-aryl imines. Further studies aimed to deep in the mechanism of this reaction, as well as to analyze the scope of the present Ru complexes in the hydrogenation of other imine types, are currently in progress.

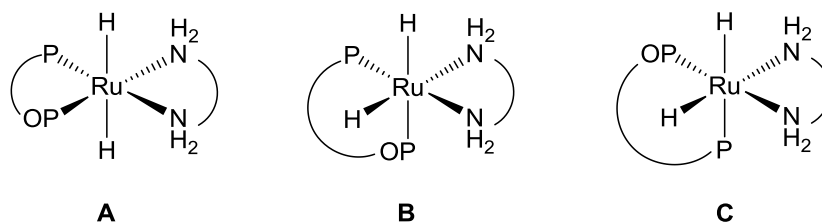


Figure 4

## Experimental Section

**Representative Procedure for Catalytic Hydrogenation Reactions.** In a glovebox, a Fischer-Porter vessel (80 mL) was charged with the appropriate imine **4** (0.88 mmol), Ru complex **1** (1.8  $\mu$ mol), <sup>t</sup>BuOK (2.0 mg, 0.018 mmol) and toluene (0.88 mL). The reactor was purged three times with H<sub>2</sub> and finally pressurized at 4 atm. After the desired reaction time, the reactor was slowly depressurized and the solution obtained evaporated. The resulting residue was analyzed by <sup>1</sup>H NMR for the determination of conversion, dissolved in CH<sub>2</sub>Cl<sub>2</sub> (2 mL), treated with 2 mL of a 2M aqueous solution of HCl and the resulting mixture stirred for 20 minutes. The resulting mixture was treated NaHCO<sub>3</sub> (3 mL, saturated aqueous solution), phases separated and the organic layer dried over magnesium sulfate. Evaporation of the resulting solution yielded amine **5**. Enantiomeric excess was analyzed by chiral HPLC.

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