CHEMISTRY
A EUROPEAN JOURNAL

ChemPubSoc
Europe

DOI: 10.1002/chem.201203193

Highly Enantioselective Imine Hydrogenation Catalyzed by Ruthenium Phosphane–Phosphite Diamine Complexes

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Dedicated to Professor José Gimeno on the occasion of his 65th birthday

The exceedingly high performance of $[RuCl_2(diphosphane)(diamine)]$ complexes in the asymmetric hydrogenation of ketones[1] has led to a great interest in the reactivity of Ru^{II} complexes based on phosphorus and amino ligands. Thus, a wide diversity of structurally related chiral complexes (e.g., $[RuX_2(P{-}P)(N{-}N)]$, $[RuX_2(P)_2(N{-}N)]$, $[RuX_2(P{-}N)_2]$; X = anionic ligand) has been described.[2] Most notably, these compounds have displayed a rich reactivity, providing active catalysts for the hydrogenation of different types of substrates.[3–5] In addition, applications of these complexes in catalytic transfer hydrogenation,[6] cycloaddition,[7] conjugate addition,[8] or hydrocyanation reactions[9] have also been reported.

Due to the industrial importance of chiral amines, an interesting application of the aforementioned Ru complexes is the asymmetric catalytic hydrogenation of imines.[10] Because the best enantioselectivities for these substrates are normally achieved with Ir catalysts,[11] a general goal in this area is the development of catalysts based on less costly metals.[12] In this regard, the group of Morris has reported that several Ru hydrides give active catalysts for imine hydrogenation reactions, and BINAP complexes with DPEN (1,2-diphenylethylenediamine) or DACH (1,2-diaminocyclohexane) diamines gave moderate enantioselectivities.[5] Moreover, Cobley and co-workers, by 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.[13] Very recently, Ohkuma et al. described a highly efficient catalyst based on Xyl-skewphos and DPEN ligands for the hydrogenation of a wide range of imines.[14]

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201203193.

A remarkable feature of $[RuX_2(P{-}P)(N{-}N)]$ complexes is the presence of four tunable, coordinating P and N groups, which offer rather unlimited possibilities for catalyst optimization. Among the possible combinations, and particularly appealing for practical reasons, are those based on only one chiral ligand.[15] 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) has produced remarkable achievements in ketone

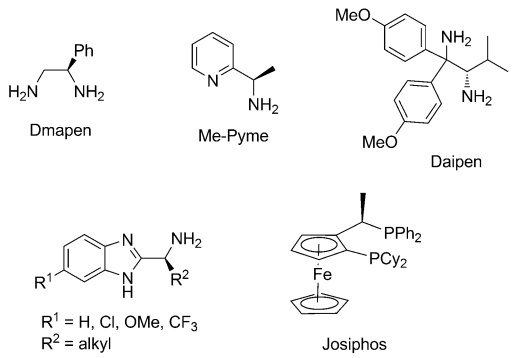
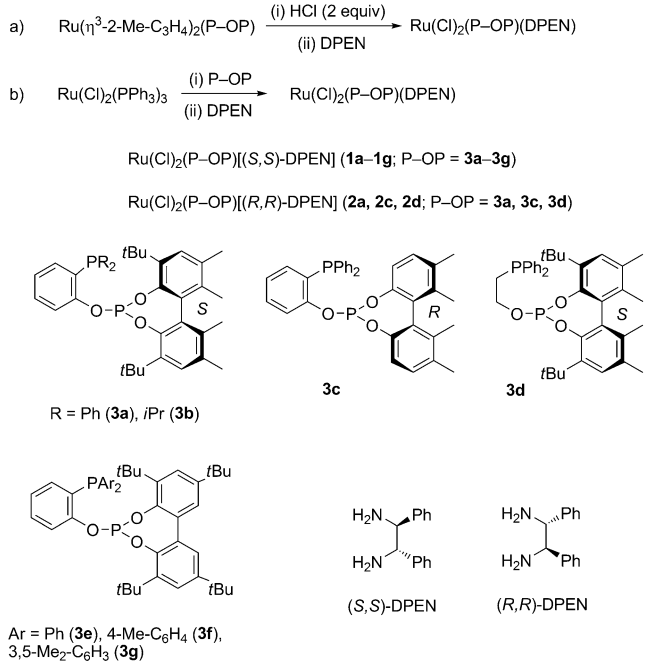


Figure 1. Some C_1 symmetric N–N′ and P–P′ ligands.

hydrogenation.[16] In contrast, the application of phosphorus ligands with two different P coordinating fragments (P–P′) is practically unexplored and is limited, to the best of our knowledge, to the diastereoselective formation of a highly active transfer hydrogenation catalyst based on a Josiphos diphosphane, as reported by Baratta et al.[6c] In this contribution we focus on the study of Ru derivatives based on P–P′ ligands. Thus, a practical and highly enantioselective catalyst, based on an achiral phosphane–phosphite and DPEN, for the catalytic hydrogenation of *N*-aryl imines is described.

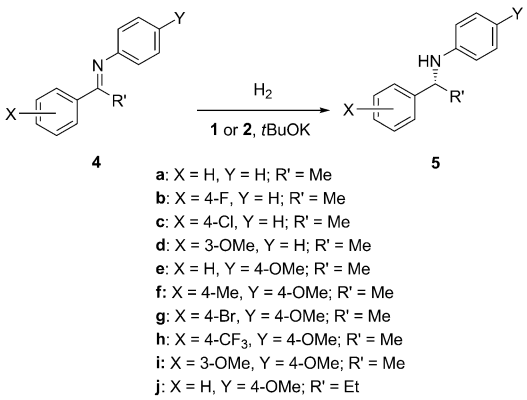
In recent years, we have studied the application of a family of chiral phosphane–phosphites (P–OP) in diverse Rh, Ru, and Ir asymmetric catalytic hydrogenations.[17] The highly modular structure of these ligands, the rich catalytic reactivity of $[RuCl_2(diphosphane)(N{-}N)]$ complexes, and the lack of phosphane–phosphite analogues in the literature

led us to investigate the preparation of some derivatives that contain P–OP ligands. Initially, the reaction of [Ru(2-Me–C_3H_4)$_2$(P–OP)][17f] with two equivalents of HCl and one equivalent of (*S,S*)-DPEN yielded complexes **1a**–**1g**. Alternatively, complexes **2a**, **2c**, and **2d** were prepared by using (*R,R*)-DPEN (Scheme 1a). The treatment of [Ru(Cl)$_2$-(PPh_3)$_3$] with one equivalent of ligand **3**, followed by a stoichiometric amount of DPEN, provided easy access to the desired compounds (Scheme 1b). Depending on the nature of the 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 isomer was purified by column chromatography. In addition, the major isomer can display either a *cis*- or *trans*-dichloride coordination mode depending on the combination of the chelating ligands (see below).



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

We 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 et al. were used (i.e., substrate/catalyst = 100, *i*PrOH as solvent, 20 bar H_2, [**4a**]/[*t*BuOK] = 1, 60 °C).[13] Under these conditions, compounds **1a** and **1b** gave moderate conversions, and the diphenyl catalyst provided a significantly better enantioselectivity (Table 1, Entries 1 and 2). Moreover, precatalysts with a smaller phosphite fragment (**1c**; Table 1, Entry 3) and an ethane backbone (**1d**; Table 1, Entry 4) were also examined. None of these improved on the enantioselectivity provided by **1a**, although the ethane-bridged catalyst, probably due to a more flexible backbone,



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

Table 1. Hydrogenation of **4a** with complexes **1** and **2**.[a]

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

[a] Reactions were carried out at 60 °C by using 0.1 M solutions of substrate and *t*BuOK as the base (B); S/C/B = 100:1:100, reaction time = 72 h. Conversion was determined by ^{1}H NMR spectroscopy and enantiomeric excess by Chiral HPLC. Configuration was determined by comparison of the sign of optical rotation with literature data (see the Supporting Information).

gave a higher conversion. To examine matching effects between diamine and P–OP ligands, the diastereomeric complex **2a** was also tested. This compound produced a similar conversion and a higher enantioselectivity than **1a** (90 % *ee*; Table 1, Entry 8). These results indicate that the chiral induction is predominantly caused by the diamine ligand and that the stereogenic axis of the phosphite has a secondary role.

Following this reasoning, we examined complex **1e**, which contains a conformationally flexible phosphite fragment. We were pleased to observe that this compound produced the same enantioselectivity as **2a** with better conversion (90 % *ee*; Table 1, Entry 5). Interestingly, these results indicate that an important variable is the phosphite flexibility, which can enable a higher catalyst reactivity, whereas the use of a more rigid phosphite fragment with a stereogenic axis retards the reaction and does not improve enantioselectivity. In addition, these results allow a further optimization of the catalyst by using other achiral P–OP ligands that differ in the phosphane group. Complexes **1f** and **1g** with *p*-tolyl and xylyl phosphane substituents were examined. While the latter produced moderate levels of conversion and enantio-

selectivity (Table 1, Entry 7), the catalyst precursor **1f** provided a higher enantioselectivity than **1a**, with an important improvement in the conversion (Table 1, Entry 6).

Most remarkably, the precatalyst **1f** showed a high reactivity in toluene, enough to complete reactions under very mild conditions with lower catalyst and base loadings (room temperature, 4 bar H_2, substrate/catalyst/base = 500:1:10). Under these conditions, a 93% *ee* for the hydrogenation of **4a** was reached (Table 2, Entry 1). These results prompted

Table 2. Hydrogenation of imines **4** with complex **1f**.[a]

Entry	Substrate	H_2 [bar]	Conv. [%]	*ee* [%]	Config.[b]
1	**4a**	4	>99	93	*R*
2	**4b**	4	>99	93	–
3	**4c**	4	>99	91	*R*
4	**4d**	4	>99	92	–
5	**4e**	4	>99	95	*R*
6	**4f**	4	>99	96	*R*
7	**4g**	4	73	89	*R*
8	**4g**	10	>99	95	*R*
9	**4h**	4	26	81	*R*
10[c]	**4h**	20	>99	93	*R*
11	**4i**	4	>99	96	–
12	**4j**	4	>99	95	*R*

[a] Reactions were carried out at room temperature in toluene with *t*BuOK as the base (B); S/C/B = 500:1:10, reaction time = 24 h, and [S] = 1.0 M, unless otherwise specified. Conversion was determined by ^{1}H NMR spectroscopy and enantiomeric excess by Chiral HPLC. [b] Configuration was determined by comparison of the sign of optical rotation with literature data when available (see the Supporting Information), otherwise the optical rotation sign is provided. [c] The reaction was performed at 60 °C in *i*PrOH.

us to investigate the scope of the latter catalytic system. We were pleased to observe that diverse *N*-aryl imines **4** were hydrogenated with high levels of conversion and enantioselectivity under these reaction conditions (Scheme 2). In general, *N*-phenyl imines gave somewhat lower enantioselectivities (91–93% *ee*, Table 2, Entries 1–4), than *N*-(*p*-anisyl) imines, which provided values from 93 to 96% *ee* (Table 2, Entries 5, 6, 8, and 10–12), in good accord with previous observations.[11g,14] During this screening, we observed that the reactions of substrates **4g** and **4h** were incomplete under these conditions. However, an increase in the hydrogen pressure to 10 bar produced the amine **5g** with full conversion and a 95% *ee* (Table 2, Entry 8). In the case of the trifluoromethyl-substituted imine **4h**, the reaction in *i*PrOH at 20 bar showed full conversion with a 93% *ee* (Table 2, 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** (Table 2, Entry 12).

To gain additional information about the stereochemistry of Ru complexes, representative compounds **2d** and **1e** were structurally characterized by X-ray crystallography.[18] Both compounds show a distorted octahedral structure and it is noteworthy that they differ in the relative coordination positions of the chloride ligands. In complex **2d**, the two chloride ligands occupy positions *cis* to one another, with one of them *trans* to the phosphite group (Figure 2). In addi-

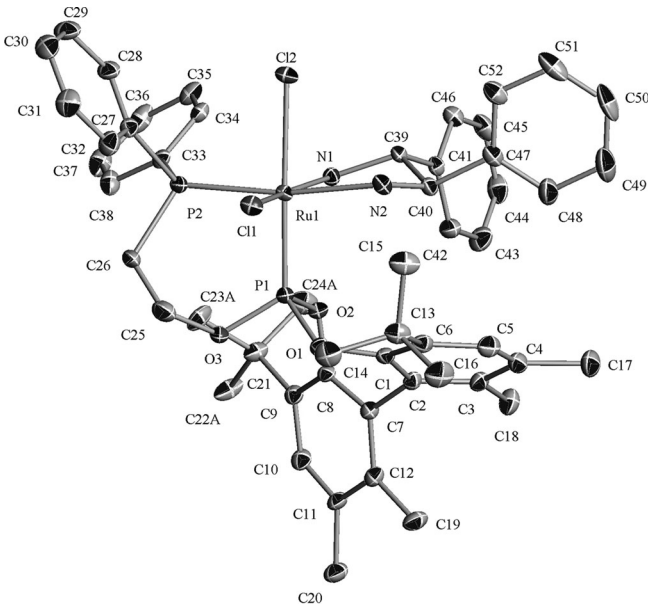


Figure 2. ORTEP view of complex **2d**. Ellipsoids are presented at the 30% probability level.

tion, this structure displays a significant *trans* influence by the phosphite group because the Ru–Cl(2) bond is appreciably longer than that of Ru–Cl(1) (2.475 and 2.409 Å, respectively). In contrast, the structure of compound **1e** shows two chloride atoms in mutually *trans* positions (Figure 3). A remarkable feature of this compound is the existence of two diastereomeric molecules in the crystal that differ in the conformation of the biphenyl fragment. The dissimilarity between the two structures is not restricted to the phosphite fragment because the change in biaryl conformation is coupled with the opposing conformations of the benzene backbone and the phosphane group. Thus, if the diamine backbone is ignored, both structures are nearly enantiomers of each other. In solution, however, only one set of signals that is composed of two doublets centered at 146.1 and 38.7 ppm [J(P,P) = 73 Hz] was observed by ^{31}P{^{1}H} NMR at room temperature. Upon cooling, the signals broadened and at −90 °C two species were observed in a 2:1 ratio. The major species appeared as two doublets centered at 149.5 and 37.3 ppm [J(P,P) = 71 Hz], whereas the minor one was characterized by two doublets at 148.8 and 36.9 ppm [J(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 that contain this phosphite fragment.[19] Therefore, the chiral diamine does not efficiently favor a phosphite biaryl conformation, which has been observed before in the case of complexes based on conformationally flexible diphosphanes.[20]

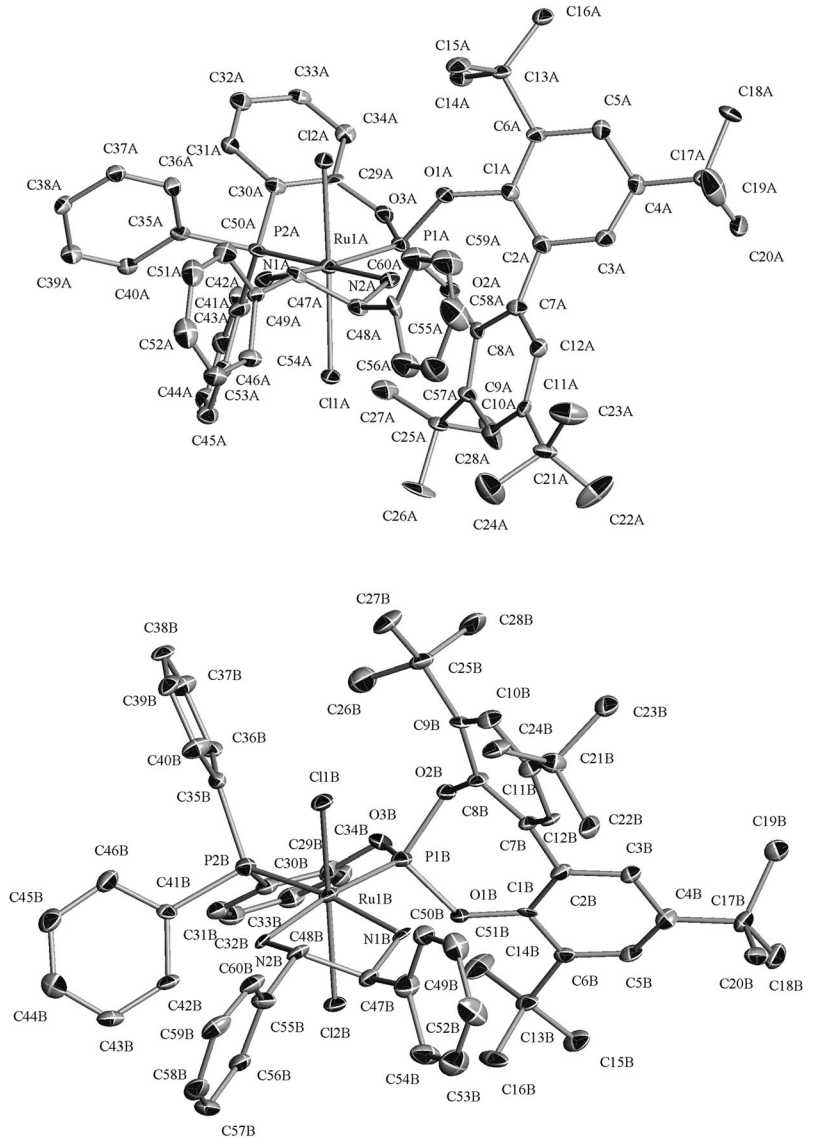


Figure 3. ORTEP views of S_a (top) and R_a (bottom) conformers of **1e**. Ellipsoids are presented at the 30% probability level.

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

Therefore, a new catalytic system for the hydrogenation of imines that is based on Ru complexes with phosphane–phosphite and diamine ligands has been described. From a ligand screening, a practical catalyst that possesses a conformationally flexible phosphane–phosphite and a DPEN ligand 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 identify 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.

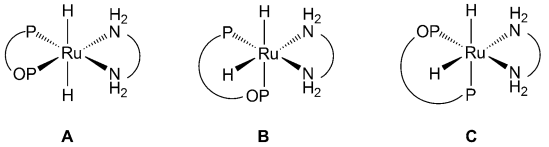


Figure 4. Structures of the dihydride complexes.

Experimental Section

General procedure: In a glovebox, a Fischer–Porter vessel (80 mL) was charged with the appropriate imine **4** (0.88 mmol), Ru complex **1** (1.8 μmol), *t*BuOK (2.0 mg, 0.018 mmol) and toluene (0.88 mL). The reactor was purged three times with H_2 and then pressurized at 4 bar. After the desired reaction time, the reactor was slowly depressurized and the solution that was obtained was evaporated. The resulting residue was analyzed by ^{1}H NMR spectroscopy for the determination of conversion,

then dissolved in CH_2Cl_2 (2 mL), treated with a 2 M aqueous solution of HCl (2 mL), and the resulting mixture was stirred for 20 min. The mixture was treated with $NaHCO_3$ (3 mL, saturated aqueous solution), the phases were separated, and the organic layer was dried over magnesium sulfate. Evaporation of the resulting solution yielded amine **5**. Enantiomeric excess was analyzed by chiral HPLC.

Acknowledgements

We acknowledge MINECO (CTQ2009–11867 and CONSOLIDER-INGENIO CSD2007–00006, FEDER support) and Junta de Andalucía (2008/FQM-3830) for financial support. M.V. thanks MINECO for a FPI fellowship and G.B. for a Marie Curie Postdoctoral Contract (PITN 2008–215193).

Keywords: asymmetric catalysis · hydrogenation · imines · P-ligands · ruthenium

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Received: September 7, 2012
Published online: November 7, 2012

