ChemPubSoc Europe

DOI: 10.1002/chem.201405276

CHEMISTRY
A European Journal
Communication

Asymmetric Hydrogenation

Highly Enantioselective Hydrogenation of *N*-Aryl Imines Derived from Acetophenones by Using Ru–Pybox Complexes under Hydrogenation or Transfer Hydrogenation Conditions in Isopropanol**

Estefanía Menéndez-Pedregal,[b] Mónica Vaquero,[a] Elena Lastra,[b] Pilar Gamasa,*[b] and Antonio Pizzano*[a]

Abstract: The asymmetric reduction of *N*-aryl imines derived from acetophenones by using Ru complexes bearing both a pybox (2,6-bis(oxazoline)pyridine) and a monodentate phosphite ligand has been described. The catalysts show good activity with a diverse range of substrates, and deliver the amine products in very high levels of enantioselectivity (up to 99%) under both hydrogenation and transfer hydrogenation conditions in isopropanol. From deuteration studies, a very different labeling is observed under hydrogenation and transfer hydrogenation conditions, which demonstrates the different nature of the hydrogen source in both reactions.

The asymmetric hydrogenation of imines is a reaction of great importance owing to the vast range of applications that chiral amines have in the pharmaceutical and agrochemical industries.[1] This has fueled a great deal of interest in this hydrogenation reaction, and studies covering the application of diverse types of Ti, Fe, Ru, Rh, and Ir catalysts have been described.[2] Despite an apparent simplicity, the hydrogenation of imines is a challenging transformation because the high levels of efficiency and broad scope that have been achieved in the asymmetric hydrogenation of olefins and ketones have not yet been accomplished.

A more appealing, safer approach to the hydrogenation of imines is the use of isopropanol as the hydrogen donor.[3] This procedure avoids the use of costly high-pressure equipment, and the nature of the by-products formed may be more favorable than the $HCOOH/NEt_3$ mixture.[4] The valuable utility of isopropanol in the asymmetric transfer hydrogenation of ketones is well known,[5] but less success has been reported in the reduction of imines. Yus et al. have exploited the synthetic potential of the diastereoselective reduction of *N*-sulfinyl imines by using Ru catalysts.[6] Alternatively, the groups of Morris[7] and Beller[8] have described the highly enantioselective Fe-catalyzed reduction of activated *N*-phosphinyl imines in the presence of tetradentate N_2P_2 chiral ligands. Notably, these catalysts did not show activity in the reduction of important *N*-aryl ketimines.[2b–j] Likewise, Cahard and Dai have described the catalytic asymmetric transfer hydrogenation of trifluoromethyl aryl ketimines by using a Ru–arene complex, which contained an amino-alcoxide ligand.[9] However, low activity was observed for the reduction of the less electrophilic methyl analogues with this catalyst. To the best of our knowledge, the practical reduction of *N*-aryl imines by using isopropanol is limited to non-asymmetric reactions. For example, Backvall et al. have described the application of the Shvo catalyst,[10] and reductions catalyzed by $[RuH(NH_3)(PMe_3)_4]$ have been reported by Yamamoto.[11] A protocol for the enantioselective transfer hydrogenation of the *N*-aryl imines in isopropanol has not yet been developed, but this would be highly desirable.

In a previous study, some of us described the extremely high activity of Ru complexes, bearing pybox (2,6-bis(oxazoline)pyridine) and monodentate P-ligands, in the transfer hydrogenation of ketones.[12] We now describe the application of these complexes in the highly enantioselective reduction of *N*-aryl imines under both hydrogenation and transfer hydrogenation conditions.

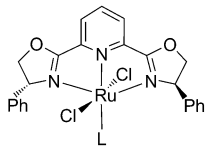
Following a preliminary screen (see Table 1) we became interested in a set of Ru complexes bearing pybox and monodentate phosphane and phosphite ligands (Figure 1). These complexes were simply prepared by reaction of the corresponding ethylene complex *trans*-$[Ru(Cl)_2(R\text{-pybox})(C_2H_4)]$ (R-pybox = Ph-pybox (**1a**), Ind-Pybox (**2a**)) with an excess of the P-ligand. By using this procedure, novel complexes **1e**, **1f**, **1g**, **2d**, and **2g** were prepared; complexes **1b**–**1d** are already known.[12] Examination of the NMR spectra indicated that all the new compounds were obtained as *trans*-isomers.

[a] *Dr. M. Vaquero, Dr. A. Pizzano*
Instituto de Investigaciones Químicas (IIQ) and
Centro de Innovación en Química Avanzada (ORFEO-CINQA)
CSIC and Universidad de Sevilla
Américo Vespucio 49, 41092 Sevilla (Spain)
E-mail: pizzano@iiq.csic.es

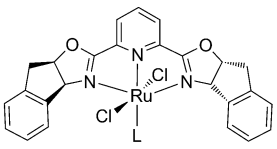
[b] *E. Menéndez-Pedregal, Dr. E. Lastra, Prof. P. Gamasa*
Laboratorio de Compuestos Organometálicos y Catálisis
(Unidad Asociada al CSIC)
Departamento de Química Orgánica e Inorgánica
Instituto de Química Organometálica "Enrique Moles"
Universidad de Oviedo, 33006 Oviedo (Spain)
E-mail: pgb@uniovi.es

[**] *Pybox = 2,6-bis(oxazoline)pyridine*

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201405276.



L = C_2H_4 (**1a**), PPh_3 (**1b**), $PMePh_2$ (**1c**), $P(OMe)_3$ (**1d**), $P(OEt)_3$ (**1e**), $P(OiPr)_3$ (**1f**), $P(OCH_2)_3CEt$ (**1g**)



L = C_2H_4 (**2a**), $P(OMe)_3$ (**2d**), $P(OCH_2)_3CEt$ (**2g**)

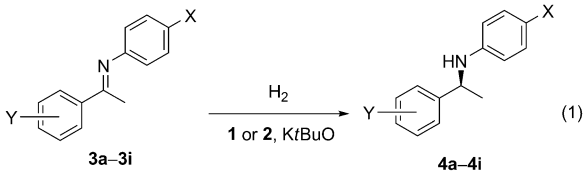
Figure 1. Ru complexes for the asymmetric reduction of imines, which contain pybox (2,6-bis(oxazoline)pyridine) and monodentate phosphane and phosphite ligands.

Table 1. Hydrogenation of **3a** with complexes **1** and **2**[a]

Entry	Catalyst precursor	Conv. [%]	*ee* of **4a** [%] (conformation)
1	**1a**	4	n.d.
2	**1b**	22	n.d.
3	**1c**	17	n.d.
4	**1d**	95	99 (*S*)
5[b]	**1d**	99	99 (*S*)
6	**1e**	99	97 (*S*)
7	**1f**	11	n.d.
8	**1g**	87	92 (*S*)
9	**2d**	95	95 (*R*)
10	**2g**	79	63 (*R*)

[a] Conditions: 20 bar H_2, 60 °C, *i*PrOH, S/C/B = 100:1:5, using KO*t*Bu as a base, 24 h. Conversion was determined by ^{1}H NMR analysis. Enantiomeric excess was determined by HPLC analysis, not determined (n.d.) for conversions below 30%. [b] Reaction performed at 70 °C with S/C/B = 500:1:5.

Initially, the hydrogenation of imine **3a** by using complexes **1** and **2** under standard reaction conditions (20 bar of hydrogen, 60 °C, S/C/B = 100:1:5, *i*PrOH, using KO*t*Bu as a base) was carried out [Eq. (1)]. The results indicated that the performance of the catalyst was very dependent upon the nature of the ligand L. Notably, the ethylene derivative **1a** (Table 1, entry 1) and the phosphane derivatives **1b** and **1c** (entries 2 and 3) gave slower reactions than their phosphite counterparts. Of the latter, $P(OMe)_3$ and $P(OEt)_3$ derivatives gave very high levels of conversion (entries 4 and 6). In contrast, the cyclic phosphite derivative **1g** offered a lower level of conversion (entry 8), which significantly decreased for the catalyst bearing the bulkier $P(OiPr)_3$ ligand (entry 7). Similarly, in the set of indenyl catalysts, the $P(OMe)_3$ derivative **2d** offered a better degree of activity compared to the $P(OCH_2)_3CEt$ derivative **2g** (entries 9 and 10). Owing to the opposite configuration of the pybox ligand, (*R*)-**4a** was predominantly produced in the reactions with complexes **2**. Regarding the enantioselectivity, complexes **1d**, **1e**, and **2d**, which contain relatively small phosphite ligands, delivered amines with the highest levels of enantioenrichment, ranging from 95 to 99% *ee*. In addition, complex **1d** was also able to complete a reaction at 70 °C with an S/C = 500, to give the amine **4a** in 99% *ee* (entry 5). Most remarkably, catalysts that were generated from **1d**, **1e**, and **2d** are the first examples of Ru catalysts without reactive NH ligand fragments (characteristic of catalysts operating by the bifunctional outer-sphere mechanism) that are used for the highly enantioselective hydrogenation of **3a**.[2j,13]



3a–3i → **4a–4i**: H_2, **1** or **2**, K*t*BuO (1)

X = H, Y = H (**3a**), 4-F (**3b**), 4-Me (**3c**), 3-OMe (**3d**)
X = 4-OMe, Y = H (**3e**), 4-Me (**3f**), 4-CF_3 (**3g**), 3-OMe (**3h**), 3,4-$(OMe)_2$ (**3i**)

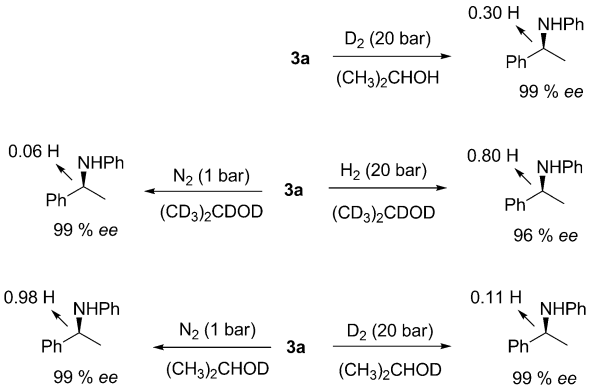
Considering that the hydrogenation reactions were performed in isopropanol in the presence of base (i.e., typical transfer hydrogenation conditions for the reduction of ketones), we were also interested in examining the reactivity of **1d** under the same reaction conditions, but under a nitrogen atmosphere. Most surprisingly, we observed full conversion of imine **3a** into amine **4a** with an exceedingly high level of enantioselectivity (99% *ee*, Table 2, entry 1). After this unexpected result, we sought to investigate whether this reactivity was more general by examining other catalyst precursors. Likewise, $P(OEt)_3$ derivative **1e** also produced full conversion to amine **4a** with a very high level of enantioselectivity (99% *ee*, entry 2). On the other hand, the presence of the cyclic phosphite in **1g** led to a small decrease in enantioselectivity (entry 3). Regarding the indenyl complexes, **2d** also produced complete conversion to give the amine **4a** with an excellent level of enantioselectivity (entry 4); whereas, the hydrogenation with **2g** was achieved in lower yield and enantioselectivity (entry 5). Notably, no reaction was observed when using phosphane catalyst **1b**.

Table 2. Transfer hydrogenation of **3a** with complexes **1** and **2**.[a]

Entry	Catalyst precursor	Conv. [%]	*ee* of **4a** [%] (conformation)
1	**1d**	>99	99 (*S*)
2	**1e**	>99	99 (*S*)
3	**1g**	84	95 (*S*)
4	**2d**	>99	99 (*R*)
5	**2g**	63	76 (*R*)
6	**1b**	0	

[a] Conditions: 60 °C, *i*PrOH, S/C/B = 100:1:5, using KO*t*Bu as a base, 24 h. Conversion was determined by ^{1}H NMR analysis. Enantiomeric excess was determined by HPLC analysis.

A comparison between the results collected in Tables 1 and 2 indicated a very close performance of $P(OMe)_3$ and $P(OEt)_3$ derived catalysts under both hydrogenation and transfer hydrogenation conditions. This similarity led us to investigate whether the reactions that were performed under hydrogen pressure were in fact transfer hydrogenation reactions. This was investigated by examining various hydrogenation reactions with deuterium-labeled reagents (Scheme 1).[14,15] As



Scheme 1. Deuteration reactions of **3a** by using **1d** as a catalyst precursor. All reactions were performed at 70 °C, S/C/B = 100:1:5 for 24 h.

a preliminary test, we examined the behavior of a 0.15 M solution of **3a** in $(CD_3)_2CDOD$ at 60 °C. Interestingly, a selective labeling of the methyl position was observed, with 95% incorporation of deuterium at this position after 24 h. This observation is indicative of an exchange of the NH proton of the enamine form of **3a** with the OD deuterium of the solvent. The hydroxyl group of the solvent also exchanges with molecular hydrogen under the hydrogenation conditions. Thus, the deuterium content of the hydroxyl group was reduced from 95 to 40% after the reaction of **3a** with catalyst precursor **1d** in $(CD_3)_2CDOD$ at 20 bar of H_2 and 70 °C. This reaction showed 20% incorporation of deuterium in the benzylic position of **4a**. In contrast, a reaction performed under the same conditions but under a nitrogen atmosphere showed 94% deuteration in the benzylic position of **4a**. On the other hand, a lower degree of deuteration (70%) was observed in the reaction performed under 20 bar of D_2 in $(CH_3)_2CHOH$. However, the aforementioned exchange between the gas phase and the solvent can reduce the deuterium incorporation at the stereogenic carbon. We therefore proceeded to examine the reaction under 20 bar of D_2 in $(CH_3)_2CHOD$. Accordingly, the extent of deuterium incorporation increased to 88%. Notably, it is interesting to compare the latter result with that obtained under transfer hydrogenation conditions in $(CH_3)_2CHOD$, which led to only 2% incorporation of deuterium. Therefore, the comparison of the deuterium incorporation in reactions performed in the presence and the absence of deuterium (both in $(CH_3)_2CHOD$ and $(CD_3)_2CDOD$) indicates the profound effect that the introduction of molecular hydrogen has on the reaction. Overall, the labeling experiments show that, under hydrogenation conditions, the main reducing agent is indeed the molecular hydrogen. Most importantly, despite the opposite deuterations that were observed, minimal variation in the levels of enantioselectivity (96–99% *ee*) were observed in these reactions.

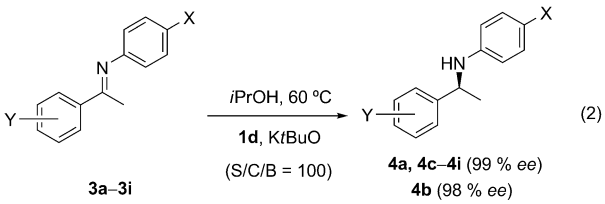
Following the outstanding results obtained in the hydrogenation of imine **3a**, we proceeded to examine the performance of complex **1d** in the hydrogenation of several aniline and *p*-anisyl imines at 60 °C and 20 bar H_2 (Table 3). *p*-F imine **3b** was hydrogenated with 92% conversion to the amine **4b** in 98% *ee* (entry 1). Likewise, *p*-tolyl substrate **3c** was reduced with 95% conversion to amine **4c** in 97% *ee*, and *m*-MeO imine **3d** produced the product **4d** in 96% *ee* (entries 2 and 3). Imines derived from *p*-anisidine also showed high levels of enantioselectivity, ranging from 98 to 99% *ee* (entries 4, 5, 7, and 8). Moreover, these substrates showed high levels of conversion to the products with the exception of **3f**, which only reacted in a moderate 67% yield (entry 5). This could be improved to 79% by carrying out the reaction at 70 °C, although a decrease on enantioselectivity was then observed (93% *ee*, entry 6).

Table 3. Reduction of imines **3** with complex **1d**.[a]

Entry	Substrate	Conv. [%]	*ee* of **4** [%] (conformation)
1	**3b**	92	98 (*S*)
2	**3c**	95	97 (*S*)
3	**3d**	91	96 (*S*)
4	**3e**	98	99 (*S*)
5	**3f**	67	98 (*S*)
6[b]	**3f**	79	93 (*S*)
7	**3g**	100	98 (*S*)
8	**3h**	100	99 (*S*)

[a] See footnote [a] of Table 1 for reaction conditions. [b] Reaction performed at 70 °C.

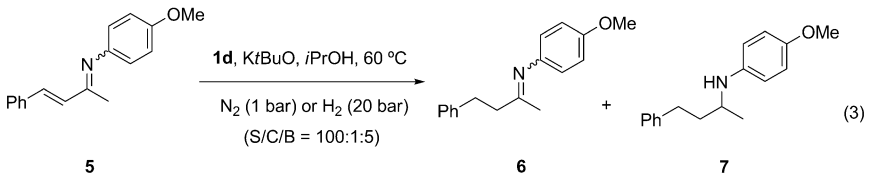
In addition, the scope of the catalyst derived from **1d** under transfer hydrogenation conditions was examined. Interestingly, the results exceeded those obtained under hydrogenation conditions. The reduction of **3b** proceeded with 93% conversion, to give the product **4b** in 98% *ee*; while the rest of imines reacted with full conversion to give the corresponding amines in 99% *ee* [Eq. (2)].



(2)

In addition, we have observed that the catalyst generated from **1d** exhibited a high degree of chemoselectivity for the reduction of the olefin in imine **5** [Eq. (3)].

Accordingly, under transfer hydrogenation conditions (60 °C, 24 h), full conversion of the substrate **5** was observed, to give a mixture of **6** and **7** in a 95:5 ratio. At the same temperature



(3)

under 20 bar of H_2, full conversion and a 70:30 ratio of **6** and **7** was obtained. Remarkably, the allyl amine was not detected in these experiments. In contrast, Morris et al. reported a significant yield of the corresponding allyl amine from the hydrogenation of the *N*-phenyl analogue of **5** by using a Ru–diphosphine diamine catalyst.[16] This observation is in accordance with the expected reactivity of a catalyst that is operating by an outer-sphere bifunctional mechanism.[17] Conversely, the data reported herein for hydrogenations catalyzed by **1** and **2** suggest an inner-sphere mechanism, which involves imine coordination. Likewise, in the asymmetric transfer hydrogenation of aryl ketones catalyzed by compounds **1**, the mechanism was proposed to involve ketone insertion (Figure 2, **A**).[12] Notably, these reactions gave the same stereochemical outcome as we observe here, and catalysts with (*R,R*)-Ph-pybox ligands provide *S* alcohols and amines.[12] Moreover, an inner-sphere mechanism, for the reduction of ketones under both hydrogenation and transfer hydrogenation conditions, has also been proposed by Plietker et al. to operate via a cationic Ru-hydride intermediate bearing a tetradentate diphosphane diamine ligand lacking NH groups.[18]

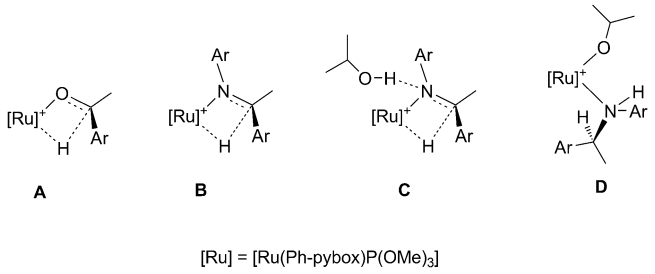


Figure 2. Proposed intermediates **A–D** in the Ru-catalyzed hydrogenation of ketones and imines.

A prominent feature of the present catalytic system derives from the very similar levels of enantioselectivity that were obtained under hydrogenation and transfer hydrogenation conditions. This observation strongly suggests a common enantio-determining step for the two processes. Based upon the above comments, with the caution imposed by the complexity of the system, we tentatively propose the imine insertion into the Ru–H bond to be the key enantio-determining step (Figure 2, **B**). Moreover, as mechanistic studies have demonstrated the participation of the OH group of the cyclopentadienyl ligand in the reduction of imines catalyzed by the Shvo catalyst,[19,20] coordination to the solvent in the imine insertion step may also be proposed (**C**). Either from the intermediate **C** or by reaction with *i*PrOH of the amide complex generated from **B**,[21] species **D** would then be formed. Finally, the subsequent steps in the catalytic cycle can reasonably be outlined from the available information in the literature.[22] Thus, facile amine decoordination in **D**[23] would produce the corresponding unsaturated alkoxide $[Ru(O\textit{i}Pr)(Ph\text{-}pybox)(P(OMe)_3)]^+$; which, under either hydrogenation or transfer hydrogenation conditions, would generate the starting hydride $[Ru(H)(Ph\text{-}pybox)(P(OMe)_3)]^+$.[24]

In summary, a highly enantioselective catalytic system, based on Ru complexes bearing pybox and monodentate phosphite ligands, for the reduction of *N*-aryl imines derived from acetophenones is reported. The catalyst remarkably shows very high levels of enantioselectivity, using either hydrogen gas or isopropanol as proton sources. The very similar performance observed under both reaction conditions point to a common active catalyst for the two types of transformations. Therefore, the present study provides the first description of an asymmetric hydrogenation/transfer hydrogenation protocol for the reduction of imines.[25] Further studies to investigate the mechanism and broaden the scope of this catalytic system are currently in progress.

Acknowledgements

Junta de Andalucía (2009/FQM-4832) and MICINN (CTQ2011-26481) are acknowledged for financial support. E.M.P. thanks the FICYT (Principado de Asturias) for a Ph.D. fellowship.

Keywords: amines · asymmetric catalysis · hydrogenation · ruthenium · transfer hydrogenation

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[23] In a detailed study of a cationic Ru catalyst for hydrogenation based on an amino-carbene ligand, an inner-sphere pathway and a key amine dissociation step, facilitated by the alcoxide ligand, have been proposed (Ref. [17a]). In the present case, the absence of chelation should also favor the release of the amine product.
[24] In the hydrogenation and transfer hydrogenation of ketones catalyzed by the Ru tetradentate diphosphane diamine complex, similar alkoxides have been postulated as intermediates (Ref. [18]). From the latter, regeneration of the hydride by β-elimination (transfer hydrogenation) or by reaction with hydrogen (hydrogenation) have been proposed.
[25] Several cases of catalysts promoting both hydrogenation and transfer hydrogenation of ketones are known, see: a) V. Rautenstrauch, X. Hoang-Cong, R. Churlaud, K. Abdur-Rashid, R. H. Morris, *Chem. Eur. J.* **2003**, *9*, 4954 – 4967; b) Ref. [15b]; c) W. Baratta, M. Ballico, G. Chelucci, K. Siega, P. Rigo, *Angew. Chem. Int. Ed.* **2008**, *47*, 4362 – 4365; *Angew. Chem.* **2008**, *120*, 4434 – 4437.

Received: September 15, 2014
Published online on November 20, 2014