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Chiral Rh phosphine-phosphite catalysts immobilized on ionic resins for the enantioselective hydrogenation of olefins in water

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The asymmetric hydrogenation of prochiral enamides with Rh complexes bearing chiral phosphine-phosphite ligands (P-OP) supported on sulphonated polystyrene resins has been studied. The complexes have been supported by simple treatment of preformed [Rh(diolefin)(P-OP)](BF_4) with the Li salt of resin. In MeOH, high enantioselectivities were observed in the hydrogenation of methyl α-*N*-acetamido acrylate (**4a**), while they decreased for less reactive methyl α-*N*-acetamido cinnamate (**4b**). Moreover, a significant Rh leaching was observed in these reactions. In contrast, a low Rh leaching was observed in reactions performed in water. Catalyst optimization enabled by the highly modular structure of P-OP ligands, led to efficient catalysts for the hydrogenation of **4a** and **4b** in water, with enantioselectivities over 95 % ee and S/C values up to 2300 and 500, respectively. To investigate the synthetic potential of the present catalytic system, the hydrogenation of a set of β-aryl α-dehydroaminoacids (**4c**-**4j**) in water has also been studied. For these reactions good catalytic activity and high enantioselectivity (87-97 % ee) were also observed. In the case of brominated substrates **4i** and **4j** an unexpected debromination reaction in water has been observed. This phenomenon seems associated to the use of the supported catalyst and water and could be minimized by the use of catalyst formed from **3f**. In addition, gel-phase $^{31}P\{^{1}H\}$ NMR studies performed with a representative supported complex show an analogous reactivity to that displayed by its soluble tetrafluoroborate counterpart. Finally, a selective deuterium labelling of product has been observed in hydrogenations of **4a** and **4b** in D_2O, similar to that observed in the homogeneous hydrogenation of these enamides with water soluble catalysts.

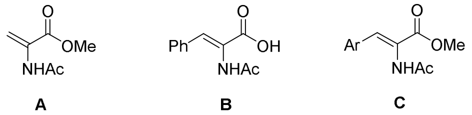
Introduction

Rhodium catalyzed enantioselective hydrogenation of olefins is a highly practical and versatile tool for the synthesis of chiral compounds.[1] Due to the broad scope and outstanding performance the corresponding catalysts have reached, a plethora of optically active compounds have efficiently been prepared by this hydrogenation.[2] This transformation has frequently been included in multi-step synthesis by the fine-chemical and pharmaceutical industries.[3] This widespread use therefore raises the interest in environmentally related and practical aspects of this transformation, often relegated by other fundamental aspects. In connection with this, it should be recalled the challenge that the mentioned industrial sectors face to decrease the environmental impact of their production.[4]

Hydrogenations of this kind are usually run with homogeneous catalysts in methylene chloride or methanol solutions, while the catalyst separation step is frequently done in a less polar organic solvent. Accordingly, the development of catalytic systems operating in water constitutes a highly interesting goal as water is a cheap, non-toxic and non-flammable solvent.[5] Moreover, the generally low solubility of hydrogenated products in water, may also enable an straightforward product separation.[6]

The attainment of efficient asymmetric olefin hydrogenations in water is, however, a rather challenging goal and only very rare cases of highly enantioselective reactions in neat water have been described in the literature.[7] This fact is in clear contrast with the outstanding results these hydrogenations have often shown in conventional organic solvents. However, the use of water as a reaction medium may introduce deep changes in the catalytic system. Hydrophobic effects and hydrogen bonding interaction with the substrate and catalytic intermediates caused by water,[8, 9] as well as the low solubility of hydrogen in this solvent may have an important influence in the reaction. Moreover, reaction of water with catalytic intermediates (e.g. by coordination or by protonation/deprotonation steps),[10] may provide alternative reaction pathways to the catalytic cycle operating in organic solvents,[11] with a potential erosion of enantioselectivity.

Extensive research pursuing efficient hydrogenation reactions in water following different approaches has been described in the literature.[12] Among them, those based on water soluble catalysts, either by ligand modification with suitable functional polar groups[13] or by attaching them to a water soluble carrier,[14] have been covered thoroughly. However, these catalysts generally display a worse performance than the parent non water-soluble ones in organic solvents.[15] Moreover, a perusal of the literature depicts a rather narrow scope of water-soluble catalysts. Thus, high enantioselectivities have been achieved in the reduction of water soluble substrates like methyl α-*N*-acetamido acrylate (**A**, 99 % ee)[7c] or α-*N*-acetamido cinnamic acid (**B**, 94 % ee),[7a] while lower values have been reported for less soluble substrates.[15, 16] For instance, in the hydrogenation of prototypical methyl α-*N*-acetamido cinnamate (**C**, Ar = Ph), the highest value obtained in neat water is 88 % ee,[16c] while 89 % ee has been reported for a CH_2Cl_2/H_2O (1:1) system.[16a] In contrast, addition of surfactants allow the reaction to occur in micelles, which may produce a dramatic increase in catalyst activity and enantioselectivity, even in the case of low soluble olefins.[17] For instance, the Group of Oehme has reported enantioselectivities up to 97 % ee in the hydrogenation of methyl α-*N*-acetamido cinnamate derivatives **C**.[17c]



Structures **A**-**C**

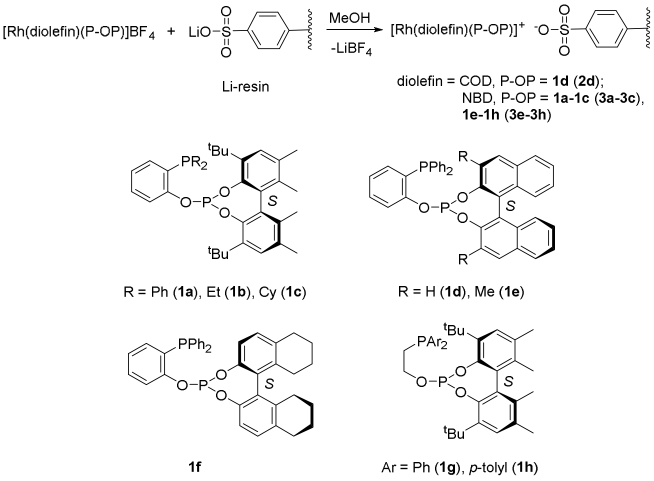
An appealing approach to perform these reactions in water is the immobilization of homogeneous catalysts on a hydrophilic support. Moreover, the heterogeneous nature of the system should enable a simple product isolation, with potential advantages over procedures based on biphasic systems or surfactants. However, immobilized catalysts have mostly been studied in conventional organic solvents,[18] while the information about their performance in water is very limited.[19] A remarkable study in this context, reported by Sheldon and coworkers, describes high activities and enantioselectivities up to 96 % ee in the hydrogenation in water of **A** using a Rh phosphoramidite catalyst immobilized on different supports.[19g] Particularly good results were obtained with diverse inorganic supports (TOF up to 750 h^{-1} and 96 % ee), while the performance decreased for catalysts supported on Na-Nafion (TOF up to 270 h^{-1} and 92 % ee), which was attributed to a poor swelling of the resin in water. In this regard, immobilization on ion exchange resins is an approach of great interest due to the high swelling in water of these materials.[20] Diverse precedents of Rh catalysts with chiral P-ligands immobilized onto exchange resins, as well as their successful application to the asymmetric hydrogenation of olefins in MeOH can be found in the literature.[21] However, the relevance of such supported catalysts for reactions performed in water has not been substantiated yet. Interestingly, a study about the application of water soluble Ir catalysts supported on exchange resins in the non-asymmetric hydrogenation of N-heterocyclic substrates in water has recently been reported.[22]

In this contribution we present a study on the immobilization of cationic rhodium complexes based on chiral phosphine-phosphite ligands[23] on an ion exchange resin. Enabled by a high swelling of the resin in water, the corresponding catalysts show good catalyst activity in this medium, while a highly enantioselective catalyst, efficient for both solutions of **A** and slurries of **C** in water, was found by a modular approach. Finally, complementary information obtained by gel-phase $^{31}P\{^1H\}$ NMR about the reactivity of supported complexes under hydrogenation conditions is also presented.

Results and discussion

Preparation of supported catalysts

Rhodium catalysts based on phosphine-phosphite ligands have become an important class of catalysts for the asymmetric hydrogenation of olefins. Thus, these catalysts have provided excellent results in the reduction of diverse type of substrates like unsaturated phosphonates, enamides of enol-esters.[24] Considering this synthetic utility, the development of supported versions of rhodium phosphine-phosphite catalysts appears to be a particularly interesting goal. Towards this, a simple approach that does not require a further ligand modification is highly desirable. In this respect, non-covalent immobilization on an ionic resin is ideal as it can directly be performed with the homogeneous catalyst precursor by a simple anion exchange.[20] It should also be stressed that this approach is limited to solvents that produce a good swelling of the resin, typically alcohols and water. Thus, by stirring a solution of complex $[Rh(diolefin)(P\text{-}OP)](BF_4)$ (diolefin = COD, NBD; P-OP = **1a-g**)[23c, 24a-b] over a sulfonated gel-type resin (Dowex 50WX2-100, 2% cross-linked, 4.8 mequiv./g exchange capacity) as its lithium salt (herein abbreviated as Li-resin, Scheme 1) the corresponding supported catalyst precursor was

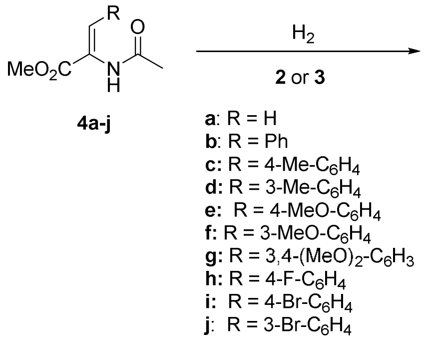


Scheme 1 Preparation of immobilized complexes.

prepared [diolefin = COD, P-OP = **1d** (**2d**); NBD, P-OP = **1a** (**3a**), **1b** (**3b**), **1c** (**3c**), **1e** (**3e**), **1f** (**3f**), **1g** (**3g**), **1h** (**3h**)]. It is worth noting that the incorporation of the Rh complex into the resin was moderate to high and ranged from 61 to 87 % (see experimental). This accounts for values between 1.6 and 2.2 % of the sulphonic groups of the resin bound to $[Rh(diolefin)(P\text{-}OP)]^+$ cations.

Hydrogenations in methanol

In the initial stage of the study, we examined the performance of representative catalyst precursors in the prototypical hydrogenation of methyl α-*N*-acetamido acrylate (**4a**, Scheme 2) in methanol under standard conditions (4 bar of H_2, room temperature). Thus, we observed full conversion and an excellent enantioselectivity using complex **3a** (99 % ee; entry 1, Table 1). This catalyst showed lower activity, while maintaining constantly high enantioselectivity upon recycling, as 87 % (99 % ee) and 78 % (99 % ee) conversions were obtained in the second and third cycles, respectively (entries 2, 3). Moreover, the same catalyst exhibited good activity although somewhat lower enantioselectivity at a lower catalyst loading (entry 4).



Scheme 2 Hydrogenation of enamides.

For comparison, we tested catalyst precursors bearing PEt_2 (**3b**) and PCy_2 (**3c**) groups, although they were significantly less enantioselective than **3a** (entries 5, 6). On the other hand, binaphthyl based complex **2d** provided 80 % ee and a good activity (entry 7). Upon recycling, activity was maintained while a severe drop on enantioselectivity was observed in the second and third cycles (entries 8, 9). This catalyst provided full conversion and a significant decrease on enantioselectivity at a lower catalyst loading (66 % ee, S/C = 600, entry 10). These results seem to indicate that a slight degradation of the catalyst generated from **2d** in methanol occurs leading to a species featured by a less effective asymmetric transfer. Finally, good activity and a moderate enantioselectivity was obtained with ethane bridged complex **3g** (83 % ee, entry 11).

After initial experiments, we turned our attention to the hydrogenation of methyl α-acetamido cinnamate (**4b**) as a representative substrate for the synthesis of important β-aryl-α-aminoacid derivatives.[25] Initially, low conversion (40 %) and good enantioselectivity (94 % ee, entry 1, Table 2) was obtained with complex **3a**. In contrast, catalyst precursor **2d** showed full conversion, but rather low enantioselectivity (43 % ee, entry 2). Moreover, this catalyst provided high conversion (84 %) but an even lower enantioselectivity in a reaction performed at S/C = 600 (entry 3). Remarkably, no catalytic activity of the supernatant solution was observed when it was transferred to another reactor under hydrogen.[26] It should be noticed, in addition, that a significant Rh leaching has been observed in reactions performed in MeOH (see supporting information for details). Thus, for reactions using **2d**, 15 and 18 % were observed in the hydrogenations of **4a** (entry 7, Table 1) and **4b** (entry 2, Table 2), respectively. Moreover, in reactions with **3a** a moderate leaching was also observed. Thus, in the hydrogenation of **4a** (entry 1, Table 1) and **4b** (entry 1, Table 2), Rh leaching values of 12 and 9 % were observed, respectively. These values are higher than those reported for supported catalysts based on diphosphine and diphosphinite ligands[21] and may be connected to some degradation of the phosphite fragment in methanol under hydrogenation conditions.

Table 1 Hydrogenation of **4a** in MeOH with supported catalysts[a]

Entry	Cat.	S/C	Time[b]	% conv	% ee (Conf)
1	**3a**	80	2 (1st cycle)	95	99 (*R*)
2		80	2 (2nd cycle)	87	99 (*R*)
3		80	3 (3rd cycle)	78	99 (*R*)
4	**3a**	320	14	>99	94 (*R*)
5	**3b**	70	2	43	35 (*R*)
6	**3c**	70	2	97	48 (*R*)
7	**2d**	60	2 (1st cycle)	>99	80 (*R*)
8		60	2 (2nd cycle)	>99	73 (*R*)
9		60	2 (3rd cycle)	>99	60 (*R*)
10	**2d**	600	16	>99	66 (*R*)
11[c]	**3g**	100	14	>99	83 (*R*)

[a] Reactions were performed using the proper amounts of **4a** and resin supported complex under 4 bar H_2 at room temperature in MeOH (3 mL), unless otherwise stated. Conversion was determined by ^1H NMR. Enantiomeric excess analyzed by chiral GC or HPLC. Product configuration was assigned by comparison with literature data. [b] Reaction time in hours. In recycling experiments, the number of the cycle is stated in brackets. [c] Reaction performed in 1 mL of MeOH.

Table 2 Hydrogenation of **4b** in MeOH with supported catalysts[a]

Entry	Cat.	S/C	Time[b]	% conv	% ee (Conf)
1	**3a**	70	14	40	94 (*R*)
2	**2d**	60	14	>99	43 (*R*)
3	**2d**	600	16	84	33 (*R*)
4	**3e**	50	14	>99	84 (*R*)

[a] Reactions were performed using the proper amounts of **4b** and resin supported complex under 4 bar H_2 at room temperature in MeOH (1 mL). Conversion was determined by ^1H NMR. Enantiomeric excess analyzed by chiral GC or HPLC. Product configuration was assigned by comparison with literature data. [b] Reaction time in hours.

Study of the model hydrogenation of 4a in water

The practical application of the present supported catalysts in methanol is strongly limited by the high Rh leaching observed and prompted us to find a more robust catalytic system. In this context, the study by Sheldon and coworkers highlighted above also reported a high metal leaching in hydrogenations of **4a** in methanol with a Rh-phosphoramidite catalyst supported on Nafion. Moreover, this catalyst provided a significantly lower leaching and a better enantioselectivity in water.[19g] Following this precedent, we examined the behavior of catalysts precursors **2-3** in water. Initially, hydrogenation of water soluble **4a** with catalyst precursor **2d** at S/C = 60 showed full conversion and 84 % ee (entry 1, Table 3). It is worth noting that this catalyst exhibited a good performance on recycling as complete reactions and constant enantioselectivities were obtained in the second and third cycles (entries 2-3). These observations contrast with the decrease in enantioselectivity observed in recycling experiments in MeOH and therefore suggest a higher stability in water of catalyst generated from **2d**. Moreover, this catalyst exhibited enough activity to finish in 24 h a reaction prepared at S/C = 600, with a moderate enantioselectivity (84 % ee, entry 4). Moreover, the reaction was also completed at S/C = 1800, but a significant decrease in enantioselectivity was observed (77 % ee; entry 5). These results clearly show a better performance of **2d** in water than in MeOH. On the other hand, **3a** showed an outstanding enantioselectivity in the hydrogenation of **4a**. Thus, for a reaction prepared at S/C = 160, 91 % conversion and 99 % ee were obtained (entry 6). A good indication of the beneficial effect of supporting the catalyst is demonstrated by the relatively poor performance of [Rh(NBD)(**1a**)](BF_4) in the hydrogenation of **4a** (S/C = 100, 4 bar H_2, room temperature), which after 24 h showed 90 % conversion and 65 % ee. In addition, a satisfactory behavior upon recycling was observed for **3a**, affording high conversion and enantioselectivity (91-96 % ee, entries 7-9). Interestingly, a lower enantioselectivity was observed in the first cycle. This phenomenon has already been reported and appears to be related to a lower enantioselectivity in the initial step of the reaction or during the activation process.[21a] Moreover, a reaction prepared at S/C = 2300 showed 80 % conversion and 99 % ee after 24 h, while full conversion and 99 % ee was observed after 72 h (entry 10). On the other hand, as observed in MeOH reactions, the substitution of the PPh_2 group by a PCy_2 fragment has a detrimental effect. Thus, catalyst precursor **3c** provided 88 % conversion and a low enantioselectivity (47 % ee, entry 11), well below results provided by **3a**.

Following the dissimilar performance of **2d** and **3a**, we rationalized that the use of a phosphite fragment with intermediate steric properties could provide a better catalyst. Complex **3e**, characterized by a binaphthyl fragment with methyl substituents at positions 3 and 3', was accordingly prepared and tested. We were delighted to observe that the corresponding catalyst showed both good activity and enantioselectivity. Thus, it finished in 24 h a reaction prepared at S/C = 100 with 97 % ee (entry 12). Moreover, this catalyst exhibited enough activity to complete reactions prepared at S/C ratios of 500 and 1500 with 96 and 93 % ee (entries 13, 14), respectively. Most remarkably, very low Rh leaching (lower than 0.8 %) was observed in both reactions. In addition, this catalyst maintained a good performance upon recycling. Thus, full conversion was obtained in three cycles while the enantioselectivity observed in the first cycle (89 % ee, entry 15) improved up to 94 and 95 % ee in the second and third cycles, respectively (entries 16-17). It is also interesting to note that **3e** displayed a significantly better performance in water than in MeOH (entry 4, Table 2). On the other hand, complex **3f**, characterized by a H_8-binaphthyl fragment, also exhibited a high reactivity and was able to complete a reaction at S/C = 1500. However, enantioselectivity for this reaction (88 % ee, entry 18) was slightly lower than that provided by **3e**. Finally, complex **3g**, possessing an ethane bridged ligand, also provided full conversion and a good enantioselectivity (89 % ee, entry 19). It did not improve, however, the value provided by the corresponding benzene bridged complex **3a**.

Table 3 Hydrogenations of **4a** in water with complexes **2** and **3**[a]

Entry	Cat.	S/C	Time[b]	% conv	% ee (Conf)
1	**2d**	60	2 (1st cycle)	>99	84 (*R*)
2		60	2 (2nd cycle)	>99	83 (*R*)
3		60	2 (3rd cycle)	>99	83 (*R*)
4	**2d**	600	16	>99	84 (*R*)
5	**2d**	1800	24	>99	77 (*R*)
6	**3a**	160	2	91	99 (*R*)
7	**3a**	80	2 (1st cycle)	>99	91 (*R*)
8			3 (2nd cycle)	>99	95 (*R*)
9			4 (3rd cycle)	>99	96 (*R*)
10	**3a**	2300	24	80	99 (*R*)
			72	>99	99 (*R*)
11	**3c**	70	2.5	88	47 (*R*)
12[c]	**3e**	100	24	>99	97 (*R*)
13[c]	**3e**	500	24	>99	96 (*R*)
14[c]	**3e**	1500	24	>99	93 (*R*)
15	**3e**	50	2 (1st cycle)	98	89 (*R*)
16		50	2 (2nd cycle)	>99	94 (*R*)
17		50	2 (3rd cycle)	>99	95 (*R*)
18[c]	**3f**	1500	19	>99	88 (*R*)
19[c]	**3g**	70	24	>99	89 (*R*)

[a] Reactions were performed at room temperature in water (3 mL) using the resin supported catalyst and the proper amount of **4a** under 4 bar H_2 unless otherwise stated. Conversion was determined by ^1H NMR. Enantiomeric excess analyzed by chiral GC or HPLC. [b] Reaction time in hours. In recycling experiments, the number of the cycle is stated in brackets. [c] Reaction performed in 1 mL of water.

Hydrogenations of β-aryl-dehydroaminoacids in water

The satisfactory results obtained with **4a** committed us to study the more challenging hydrogenation of **4b** in water. This reaction is hampered by the low solubility of this compound in water (7.3 × 10^{-3} mol/L at 25 ºC),[27] as substrate amounts typically used in the present hydrogenations (0.06-0.3 mol/L, for S/C = 100-500) are well above this solubility value. As an alternative to the substrate slurry, we have initially tested a mixture of water and environmentally friendly 2-Me-thf (9:1 v/v, reaction conditions A), which is able to dissolve the required amount of **4b**. Hydrogenation of the resulting solution with catalyst precursor **2d** provided full conversion for a reaction performed at S/C = 120 with 88 % ee (entry 1, Table 4). On the other hand, precatalyst **3a** showed a very slow reaction under these conditions, with a conversion lower than 10 % in 14 h (entry 2). In contrast, **3e** provided full conversion and a remarkable 96 % ee (entry 3). Moreover, an increase in reaction temperature up to 40 ºC only caused a small decrease on enantioselectivity (94 % ee, entry 4).

As an additional approach to facilitate the hydrogenation of **4b** in water, we have considered the addition of a surfactant to disperse the substrate in the reaction media. In order not to interfere in the electrostatic catalyst immobilization, a polar surfactant instead of an ionic one was preferred. Thus, a set of reactions were prepared by adding Triton-X100 to the reaction medium (reaction conditions B).[28] Initially, a reaction under these conditions using catalyst precursor **3a** and 10 % mol of surfactant relative to substrate, showed a very slow reaction and a low conversion was observed after a prolonged reaction time (30 %, entry 5). Alternatively, the use of complex **3e** under these reaction conditions, led to complete conversion and a high enantioselectivity (96 % ee, entry 6). Moreover, a similar performance was observed at a S/C ratio of 200 (97 % ee, entry 7). In addition, a decrease by half of the amount of surfactant did not affect catalyst performance appreciably (entry 8). Moreover, an increase in temperature up to 40 ºC only produces a small decrease in enantioselectivity (95 % ee, entry 9). A further reduction of the amount of surfactant to 2.5 mol % and of the catalyst loading (S/C = 500) also showed full conversion, while enantioselectivity was reduced slightly (93 % ee, entry 10).

Table 4 Hydrogenation of **4b** with complexes **2** and **3** performed in H_2O/2-Me-thf or in H_2O/Triton-X100[a]

Entry	Cond.[b]	Cat.	S/C	Time	% conv	% ee (Conf)
1	A	**2d**	120	14	>99	88 (*R*)
2	A	**3a**	160	14	10	n.d.
3	A	**3e**	100	18	>99	96 (*R*)
4[c]	A	**3e**	100	18	>99	94 (*R*)
5	B (10 %)	**3a**	160	40	30	88 (*R*)
6	B (10 %)	**3e**	100	18	>99	96 (*R*)
7	B (10 %)	**3e**	200	18	>99	97 (*R*)
8	B (5 %)	**3e**	200	18	>99	96 (*R*)
9[c]	B (5 %)	**3e**	200	18	>99	95 (*R*)
10[c]	B (2.5 %)	**3e**	500	24	>99	93 (*R*)

[a] Reactions were performed at room temperature using the resin supported catalyst and the proper amount of **4b** in the corresponding solvent (2 mL) under 4 bar H_2 unless otherwise stated. Conversion was determined by ^1H NMR. Enantiomeric excess analyzed by chiral GC or HPLC. [b] Conditions A: reactions performed in H_2O/2-Me-thf (9:1 v/v); conditions B: Triton-X100 added, % mol relative to substrate in brackets. [c] Reaction at 40 ºC.

Considering the high water content of the swelled resin, results obtained in the hydrogenation of **4b** with catalyst precursor **3e** under conditions A and B, indicate that the supported catalyst is able to provide good catalyst activity and enantioselectivity for this substrate in an essentially aqueous reaction medium. Accordingly, we rationalized that if the substrate has some solubility in water, an effective hydrogenation of this substrate could then be effected in neat water. Thus, we next explored the hydrogenation of a slurry of **4b**.[6] Initially, complex **3a** only provided low conversion at room temperature (8 %), although the corresponding catalyst afforded very high enantioselectivity (98 % ee, entry 1, Table 5). In order to increase conversion, a reaction at 40 ºC was also explored. This provided a moderate conversion (44 %, entry 2) and a high enantioselectivity (98 % ee). An alternative experiment prepared at 40 ºC under 20 bar H_2 showed a reaction completed, although a decrease on enantioselectivity was observed (92 % ee, entry 3). In contrast, catalysts formed from **2d** and **3e** were more active and finished the reaction in 14 h at room temperature under 4 bar H_2 (entries 4, 5). Worth of noting, **3e** provided a remarkable enantioselectivity of 97 % ee. Also pertinent to note, an increase in reaction temperature up to 40 ºC had a negligible effect on enantioselectivity (entry 6). Under these conditions, complex **3f** also provided a high catalyst activity and a good enantioselectivity (91 % ee, entry 7), while **3h** offered high conversion (90 %) and an outstanding enantioselectivity (97 % ee, entry 8).

Among these catalysts, **3e** displayed a suitable performance. Initially, a reaction prepared at room temperature and S/C ratio of 500 showed high enantioselectivity (97 % ee), although the conversion was only moderate (75 %, entry 9). However, raising the reaction temperature to 40 ºC significantly increased conversion to 93 %, without an important effect on enantioselectivity (entry 10). Finally, full conversion and a remarkable enantioselectivity of 95 % ee were obtained at 50 ºC (entry 11).

To the best of our knowledge, the results presented in Table 5 provide the highest enantioselectivities to date in the hydrogenation of **4b** in neat water. Most interestingly, aside from the practical advantages associated to catalyst heterogenization, the support also has a remarkable effect on catalyst performance. Thus, the hydrogenation of **4b** in H_2O using [Rh(NBD)(**1e**)](BF_4) (S/C = 200, 4 bar H_2, 40 ºC) showed 40 % conversion and 32 % ee after 24 h. These values indicate both lower catalyst activity and enantioselectivity than provided by corresponding supported catalyst **3e**.

Table 5 Hydrogenation of **4b** with complexes **2** and **3** in neat water[a]

Entry	Cat.	S/C	Time	% conv	% ee
1	**3a**	160	14	8	98 (*R*)
2[b]	**3a**	160	24	44	98 (*R*)
3[b,c]	**3a**	160	24	>99	92 (*R*)
4	**2d**	120	14	>99	89 (*R*)
5	**3e**	100	14	>99	97 (*R*)
6[b]	**3e**	100	24	>99	96 (*R*)
7[b]	**3f**	100	24	>99	91 (*R*)
8[b]	**3h**	130	24	90	97 (*R*)
9[d]	**3e**	500	24	75	97 (*R*)
10[b, d]	**3e**	500	24	93	96 (*R*)
11[d, e]	**3e**	500	24	>99	95 (*R*)

[a] Reactions were performed at room temperature using the resin supported catalyst and a slurry of **4b** in water (1 mL) under 4 bar H_2 unless otherwise stated. Conversion was determined by ^1H NMR. Enantiomeric excess analyzed by chiral GC or HPLC. [b] Reaction at 40 ºC. [c] Reaction at 20 bar H_2. [d] Slurry in 6 mL of water. [e] Reaction at 50 ºC.

An analysis of the Rh leaching in hydrogenations of **4b** in water with complex **3e** indicates generally low values. Thus, for type A reaction conditions, Rh concentration was lower than 0.2 ppm, which corresponds to a leaching lower than 0.9 % (entry 3, Table 4). This value was however increased up to 2.4 % in the reaction performed at 40 ºC (entry 4). On the other hand, the use of 10 % mol surfactant in conditions of type B also showed values lower than 0.9 % for reactions performed at room temperature (entries 6, 7). In contrast, the metal leaching significantly increased up to 2.0 % for the reaction heated at 40 ºC (entry 9). Most remarkably, reactions performed in neat water at 40 ºC exhibited a very low metal leaching. Thus, lower values than 0.5 % were observed for reactions performed at S/C ratios of 100 and 500 (entries 6, 10, Table 5). Likewise, the Rh leaching also kept lower than 0.5 % for the reaction performed at 50 ºC (entry 11).

It is also worth to comment that a comparison of results of hydrogenations of **4a** and **4b** indicates that both the nature of phosphine and phosphite fragments have a strong impact on the catalytic hydrogenation. On one hand, catalysts bearing a PPh_2 fragment provided better results than those bearing dialkylphosphino groups. On the other, substitution of the phosphite biphenyl fragment is required for the attainment of high enantioselectivity. Moreover, the size of these substituents also has an impact on catalyst activity. Thus, *t*-Bu substituted **3a** provided the best enantioselectivities, but it displayed a lower catalyst activity. In contrast, less sterically hindered **2d** and **3f** provided higher catalyst activity but lower enantioselectivities. Among them, complex **3e** which possess phosphite steric properties between the two prior limiting cases, compromises both suitable catalyst activity and good enantioselectivity.

Having achieved good results in the hydrogenation of representative substrate **4b** in water, we investigated the asymmetric hydrogenation of related substrates **4c**-**4j**. However, to broaden the scope of the present catalytic system is not trivial, as the introduction of aryl substituents further reduces substrate solubility in water, ranging between 1.4×10^{-3} mol/L (**4j**) and 3.9×10^{-3} mol/L (**4g**) at 25 ºC.[27] Initially, hydrogenation of the *p*-Me enamide **4c** using precatalyst **3e** at 40 ºC provided full conversion and 94 % ee (entry 1, Table 6), although the catalyst was not reactive enough to complete a reaction at S/C = 250 (entry 2). On the other hand, the corresponding *m*-Me substrate **4d** produced a complete reaction with 96 % ee (entry 3). In addition, the *p*-MeO substrate **4e** provided full conversion and 95 % ee (entry 4). An increase to S/C = 250 also showed a complete reaction, while the enantioselectivity decreased down to 90 % ee (entry 5). On the other hand the *m*-MeO enamide **4f** also yielded a complete reaction and 97 % ee under our standard conditions (entry 6). In contrast to the above results, dimethoxy substrate **4g** was less reactive and only 60 % conversion was observed, although it provided a high enantioselectivity (96 % ee, entry 7). However, an increase in reaction temperature up to 50 ºC yielded full conversion without erosion on enantioselectivity (97 % ee, entry 8). Moreover, *p*-F substrate **4h** also provided good results, with full conversion and 96 % ee under our standard conditions (entry 9). It is also pertinent to comment on the visual changes produced by the reaction. Thus, hydrogenations providing low conversion clearly show the presence of remaining solid substrate (Figure 1a). In reactions with high conversion, disappearance of suspended solid is observed and product **5** can generate a new oily phase over the aqueous one (Figures 1b-1c), or apparently be dissolved in the aquatic phase (Figures 1d-1e).

In contrast with the previous reactions, *p*-Br substrate **4i** showed a different reactivity than previous enamides. Thus, a hydrogenation performed under our standard conditions afforded a product mixture (80 % conv.) composed by desired product **5i** and debrominated product **5b** in a 50:50 ratio (entry 10). On the other hand, the *m*-Br substrate **4j** showed a cleaner reaction towards the desired hydrogenated product **5j**, although it also showed an appreciable formation of **5b** in the reaction. Thus, the **5j**:**5b** ratio was 80:20 (75 % conversion, entry 11). Pursuing more selective reactions with Br substituted substrates, complex **3f** was also tested. The corresponding catalyst afforded higher conversion and selectivity, providing 80 % of **5i** and 85 % of **5j**, respectively, in the corresponding products. Moreover, enantioselectivities were only slightly lower than those provided by **3e** and values of 85 and 84 % ee, were obtained for **5i** and **5j**, respectively (entries 12, 13).

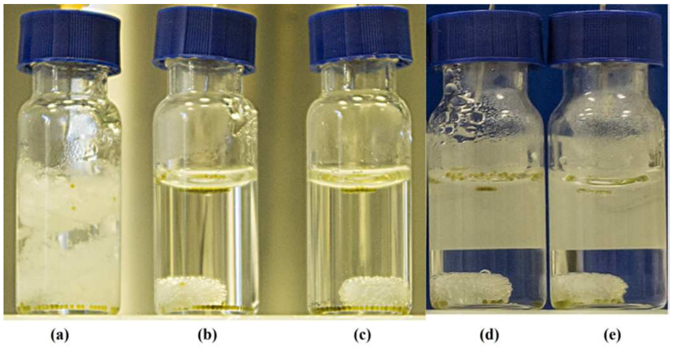


Figure 1 Photographs of vials corresponding to hydrogenations of diverse substrates **4** performed with complex **3e** (4 bar H_2, 40 °C, 24 h). (a): **4d** (S/C = 250; 40 % conv.); (b): **4d** (S/C = 100; > 99 % conv.); (c): **4e** (S/C = 250; > 99 % conv.); (d): **4b** (S/C = 100; > 99 % conv.); (e): **4a** (S/C = 100; > 99 % conv.).

In order to provide additional information about the unexpected debromination of **4i** some additional experiments were also performed. We first examined the behavior of **4i** under standard homogeneous hydrogenation conditions. Thus, complete conversion of **4i** into **5i** (99 % ee, S/C = 100, 24 h) was observed in a reaction performed with unsupported $[Rh(NBD)(\mathbf{1e})](BF_4)$ in CH_2Cl_2. Moreover, formation of **5a** was not observed in the hydrogenation of **4i** in MeOH using complex **3e** (>99 % conversion, 59 % ee, 14 h). It seems therefore that the interplay of water and the supported catalyst is required for debromination. Moreover, we have observed that **5i** can undergo the debromination reaction under hydrogenation conditions. Thus, when a solution of **5i** was exposed to 4 bar H_2 in the presence of **3e**, a mixture of **5a** and **5i** in 15:85 ratio was observed after 14 h at 40 ºC. As expected, this reaction was not observed when **3e** was substituted by the complex-free Li-resin. It is worth noting that along with the debromination we have observed a significant Li leaching of the resin, while Rh leaching remained lower than 0.5 %. Thus, for hydrogenations of **4i** and **4j** (0.06 mmol of substrate in 1 mL of water) using complex **3e** (entries 10, 12) values of $[Li] = 3.9 \times 10^{-3}$ M (22 % Li leaching) and $[Li] = 3.6 \times 10^{-3}$ M (20 % Li leaching) were obtained, respectively. As a reference value, $[Li] = 1.1 \times 10^{-3}$ M

(6 % Li leaching) was observed after the hydrogenation of **4b** under identical reaction conditions. In contrast, in the hydrogenation of **4i** with **3e** in MeOH, a negligible Li leaching was observed (0.1 %). We speculated that this leaching could be favored by the formation of HBr under hydrogenation conditions,[29, 30] which should result in the generation of **5b** from **5i** (or of **4b** from **4i**).[31] Thus, the presence of acid in the solution may produce some Li/H exchange in the resin, due to the low selectivity coefficient of Li cation on polystyrene sulphonated resin.[32] According to this, treatment of Li-resin (5.0 mg) with solutions of HBr (1.0 mL) at 40 ºC for 24 h showed a higher Li concentration when the concentration of acid was raised. Thus, when the latter grew from 0.006 M to 0.058 M, an increase in [Li] from 2.2×10^{-3} M to 7.3×10^{-3} M was observed.

Besides these experiments, due to the high enantioselectivity displayed in the hydrogenation of **4b**, we were also interested in examining the performance of complex **3h** in the hydrogenation of substrates **4c-4j**. Then, a set of reactions under standard conditions were prepared (entries 14-21). The enantioselectivities observed were generally high, between 94 and 98 % ee, with the exception of dimethoxy substituted substrate **4g**, for which a very low conversion and a value of 86 % ee was obtained (entry 18). Despite the high enantioselectivities, the catalytic activity shown by complex **3h** was however lower than that provided by **3e**.

Table 6 Hydrogenation reactions of **4c-4f** in water[a]

Entry	Subs.	Cat.	S/C	Time (h)[b]	% conv	% ee
1	**4c**	**3e**	100	24	>99	94
2	**4c**	**3e**	250	24	40	94
3	**4d**	**3e**	100	24	>99	96
4	**4e**	**3e**	100	24	>99	95
5	**4e**	**3e**	250	24	>99	90
6	**4f**	**3e**	100	24	>99	97
7	**4g**	**3e**	100	24	60	96
8[c]	**4g**	**3e**	100	24	>99	97
9	**4h**	**3e**	100	24	>99	96
10[d]	**4i**	**3e**	100	24	80	87
11[e]	**4j**	**3e**	100	24	75	88
12[f]	**4i**	**3f**	100	24	85	85
13[g]	**4j**	**3f**	100	24	95	84
14	**4c**	**3h**	130	24	50	96
15	**4d**	**3h**	130	24	90	95
16	**4e**	**3h**	130	24	55	96
17	**4f**	**3h**	130	24	65	96
18	**4g**	**3h**	130	24	15	86
19	**4h**	**3h**	130	24	80	94
20	**4i**	**3h**	130	24	25	98
21	**4j**	**3h**	130	24	50	94
22[h]	**4f**	**3e**	50	12 (1st cycle)	>99	97
23[h]			50	12 (2nd cycle)	>99	97
24[h]			50	12 (3rd cycle)	60	86
25[h]			50	12 (4th cycle)	5	n.d.

[a] Reactions were performed at 40 ºC using the resin supported catalyst and a slurry of substrate in water (1 mL) under 4 bar H_2 unless otherwise stated. Conversion was determined by ^1H NMR. Enantiomeric excess analyzed by chiral GC or HPLC. [b] In recycling experiments, the number of the cycle in brackets. [c] Reaction at 50 ºC. [d] Mixture of **5i**:**5a** products in a 50:50 ratio obtained. [e] Mixture of **5j**:**5a** products in a 80:20 ratio obtained. [f] Mixture of **5i**:**5a** products in a 80:20 ratio obtained. [g] Mixture of **5j**:**5a** products in 85:15 ratio obtained. [h] Slurry in 6 mL of water.

Finally we attempted to perform catalyst recycling in water with complex **3e**. At this regard it should be recalled that due to their low solubility, solid substrates **4b-4j** cannot be transferred as water solutions at the required concentration for the hydrogenations. Moreover, the present hydrogenation catalysts are very reactive towards oxygen, therefore recycling operations should be made under an inert atmosphere or preferably under hydrogen. Upon these considerations we devised a simple procedure to add solid substrates to the reactor inside a piece of teflon tubing (see supporting information). To test this procedure, we examined a hydrogenation of **4f**. Results obtained indicated full conversion and 97 % ee in the first and second cycles (entries 22, 23), while unfortunately, a rapid degradation in catalyst performance was observed in the third and fourth cycles (entries 24, 25). It is worth noting that Rh concentration in solution kept lower than 0.2 ppm (Rh leaching lower than 2 %) in all cycles. We therefore speculated that the loss of catalyst performance observed may be associated to the introduction of oxygen traces upon recycling. Therefore, an improved reactor design is required to implement an efficient catalyst recycling of the present catalysts in water.

Mechanistic studies

In order to provide additional information, we have monitored by gel phase $^{31}P\{^1H\}$ NMR the progress of a selected hydrogenation.[33] Initially, we observed that complex **3g** provided a spectrum of satisfactory quality in CD_3OD. In this spectrum the typical pattern for a phosphine-phosphite ligand coordinated to a rhodium atom is observed (Figure 2a). The phosphite group appears as a doublet of doublet centered at 123.6 ppm ($^1J_{RhP}$ = 259 Hz, $^2J_{PP}$ = 69 Hz), while for the phosphine, the corresponding signal appears as a doublet of doublet centered at 7.4 ppm ($^1J_{RhP}$ = 147 Hz). It is worth noting that a spectrum of the methanol supernatant only showed low intense singlets assigned to phosphorus impurities after standing 3 days at room temperature, indicating the stability of the catalyst precursor under these conditions. As expected, these data closely match the data for corresponding soluble [Rh(NBD)(**1g**)](BF_4) in CD_3OD [δ_{PO} = 123.1 (dd, *J*(P, Rh) = 257 Hz, *J*(P, P) = 68 Hz, PO), δ_{PC} = 8.7 (dd, *J*(P, Rh) = 147 Hz].

When the sample of **3g** was pressurized with 4 bar of H_2, fast reaction was detected and immediate disappearance of **3g** was observed along with the formation of new species **6g** (Scheme 3). The latter is characterized in the $^{31}P\{^1H\}$ NMR by two multiplets centred at 127.7 and 33.0 ppm (Figure 2b), corresponding to phosphite and phosphine groups, respectively (Figure 2c). Remarkably, no signals were detected in the hydride region of the ^1H NMR experiment. By comparison with the spectrum obtained after hydrogenation of [Rh(NBD)(**1f**)](BF_4) in CD_3OD, **6g** can be assigned to the supported methanol solvate. As a next step we investigated the formation of complexes of enamides **4**. Thus, addition of 3 equivalents of **4b** to **6g** showed a mixture of the latter and new species **8g** in ca. 3:1 ratio.[34] A further addition of **4b** up to 12 equivalents increased the amount of **8g** and a 0.7:1 **6g**:**8g** ratio was then observed (Figure 2d). Complex **8g** is characterized by a doublet of doublet in the coordinated phosphine region centered at 0.3 ppm ($^1J_{RhP}$ = 152 Hz, $^2J_{PP}$ = 70 Hz), while in the phosphite region signals corresponding to **6g** and **8g** overlap in a broad doublet of doublet centred at 128.2 ppm ($^1J_{RhP}$ = 246 Hz, $^2J_{PP}$ = 70 Hz). Data for **8g** are in good accord with those of soluble enamide adducts prepared in our laboratory.[23c] For further comparison, a sample of $[Rh(CD_3OD)_2(\mathbf{1g})](BF_4)$ was treated with 20 equivalents of **4b**. This showed a mixture of the deuteromethanol adduct and $[Rh(\mathbf{4b})(\mathbf{1g})](BF_4)$ in a 1:3 ratio. The latter species was characterized by phosphine and phosphite signals at δ = 0.8 ($^1J_{RhP}$ = 151 Hz, $^2J_{PP}$ = 70 Hz) and δ = 128.4 ($^1J_{RhP}$ = 243 Hz, $^2J_{PP}$ = 70 Hz), respectively (Figure 2f). Thus, an analogous behavior is observed for the immobilized and the homogeneous systems. On the other hand, an addition of 3 equiv of **4a** to **6g** showed nearly full displacement of CD_3OD by the enamide. A subsequent increase of the amount of **4a** up to 12 equiv showed full conversion into the corresponding enamide adduct **7g**. This compound show rather similar data to **8g**. Thus, **7g** is characterized by two doublet of doublet centered at δ = 2.3 ($^1J_{RhP}$ = 152 Hz, $^2J_{PP}$ = 70 Hz) and a broad doublet of doublet at δ = 127.5 with $^1J_{RhP}$ and $^2J_{PP}$ roughly ranging 230 and 70 Hz, respectively. Moreover, exposing the latter sample to 4 bar H_2 only showed the presence of the supported deuteromethanol adduct **6g**, while no intermediates in the catalytic cycle were observed. In connection with this, Reek and coworkers reported a similar observation in studies with Rh complexes bearing Indolphos ligands, which possess similar electronic properties to P-OP.[35] As a final remark, the high coordinating ability of NBD in the present system should be stressed. Thus, addition of an excess of NBD (12 equivalents) to the **6g**:**8g** mixture cleanly regenerated **3g** (Figure 2e). A similar observation was observed in the case of **8g**.

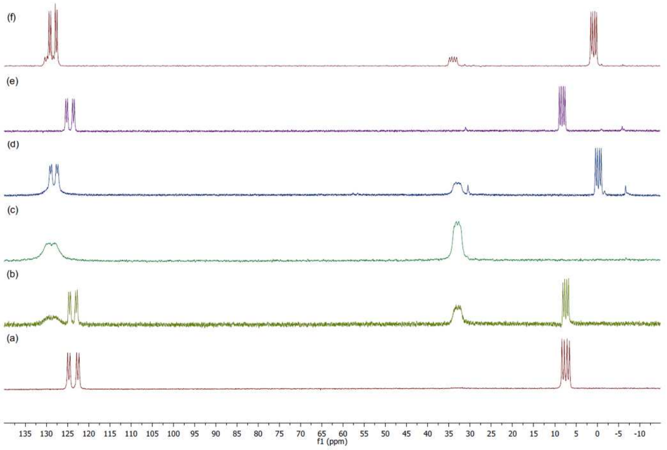
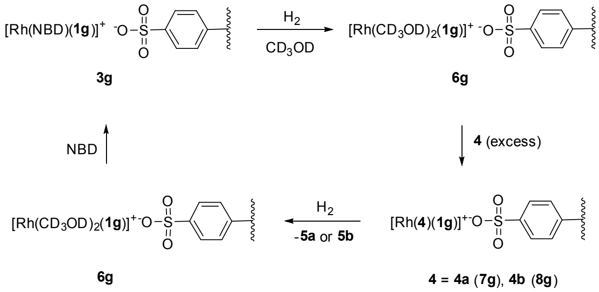


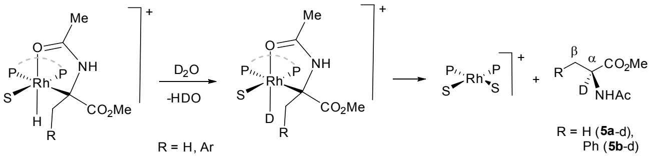
Figure 2 Gel-phase $^{31}P\{^1H\}$ NMR spectra in CD_3OD of the following samples: (a) complex **3g**; (b) after pressurizing with 4 bar H_2; (c) 0.5 h later; (d) after addition of 12 equivalents of **4b**; (e) after addition of 12 equivalents of NBD; (f) $^{31}P\{^1H\}$ NMR spectrum of sample obtained after hydrogenation of $[Rh(NBD)(\mathbf{1g})](BF_4)$ in CD_3OD followed by addition of 20 equivalents of **4b**.

The NMR study described above indicates a close similarity between the homogeneous and the resin immobilized catalytic hydrogenation systems. It should be recalled, in connection with this, that a product labelling at position α in the hydrogenation of **4a** and **4b** in D_2O using water soluble complexes has been described in the literature.[10b, 10d] This selective labeling has been proposed to result from an exchange between the hydrido-alkyl intermediate and D_2O, leading to the corresponding Rh deuteride (Scheme 4).



Scheme 3

With the intention to investigate if such effect operates in the present system, we have prepared some hydrogenations of **4b** in D_2O. Thus, the reaction with complex **2d** exhibited a deuterium labelling of 67 % in position α (entry 1, Table 7), while 9 % D was observed in position β. On the other hand, the reaction performed with complex **3e** showed 40 % D in the position α, while no labelling was observed in position β (entry 3). Finally, a smaller labelling (5 %) was observed in the reaction performed with complex **3a** (entry 2). Likewise, in hydrogenations of **4a**, a low labelling (4 %, entry 4) was observed in the reaction using **3a**, while the corresponding hydrogenation using **2d** as catalyst precursor showed a significantly higher value of deuterium incorporation in position α (75 %, entry 5).



Scheme 4 Proposed formation of deuterated **5a**-d and **5b**-d.

These results outline a similar behavior to that reported for water soluble catalysts. Moreover, in good accord with the proposed labelling mechanism involving exchange between the alkyl-hydride intermediate and water (i.e. after the generation of the stereogenic center), the enantioselectivities obtained in these reactions are very close to those obtained in H_2O. Finally, a dependence of labelling with the steric properties of the ligand, being the labelling higher with less sterically encumbered ligands has been observed. At this regard, a slower reaction with D_2O due to steric hindrance caused by the *t*-Bu substituents may tentatively be proposed to explain the results.

Table 7 Hydrogenation of **4a**-**4b** performed in D_2O[a]

Entry	Subst.	Cat.	S/C	% D (α)	% conv	% ee[b]
1	**4b**	**2d**	120	67	95	85 (83)
2	**4b**	**3a**	160	5	40	97 (98)
3	**4b**	**3e**	100	40	>99	96 (97)
4[c]	**4a**	**3a**	500	4	80	99 (99)
5[c]	**4a**	**2d**	500	75	>99	83 (84)

[a] Conditions: reactions performed at 40 ºC in D_2O for 24 h unless otherwise stated. Conversion was determined by ^1H NMR. Enantiomeric excess analyzed by chiral GC or HPLC. [b] Enantioselectivity of the corresponding reaction in H_2O in brackets. [c] Reaction performed at room temperature.

Conclusions

In this contribution we present a convenient immobilization of rhodium phosphine-phosphite catalysts on an ionic resin. The procedure is simple, as it does not require chemical modification of the readily accessible cationic rhodium complexes, and provides the supported complexes in moderate to high yield. The corresponding catalysts show a good performance in the hydrogenation of **4a** in MeOH, with enantioselectivities up to 99 % ee. On the other hand, no catalyst was found to provide both high activity and enantioselectivity in the hydrogenation of **4b** in MeOH. Moreover, a high metal leaching was observed in these reactions. In contrast, a suitable catalyst (**3e**) for the hydrogenation of **4b** in water, providing good activity and an enantioselectivity up to 97 % ee, was found following a rational approach. For this substrate, extensively studied in the literature, this is the highest value obtained in neat water. This catalyst has a broader scope and provides both good activity and enantioselectivity, between 87 and 97 % ee, in the hydrogenation of several β-aryl dehydroaminoacids (**4c**-**4j**). Thus, besides to the general advantage on an easier catalyst separation provided by immobilization, the high swelling of the resin supporting the catalyst, enables to perform efficient hydrogenations in water in the present case. Moreover, the hydrophilic support significantly enhances the performance of the catalyst in comparison with that observed by the corresponding tetrafluoroborates in water. On the other hand, in the hydrogenation of brominated substrates **4i** and **4j** an unexpected formation of debrominated **5b** was observed as a side reaction. This phenomenon seems associated with the use of both water and the Li-resin. In addition, NMR studies show a similar behavior of the supported catalysts to the homogeneous one. Likewise, a similar deuterium labelling than reported in the literature for homogeneous hydrogenation of **4a** in water, has also been observed in the present system.

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Notes and references

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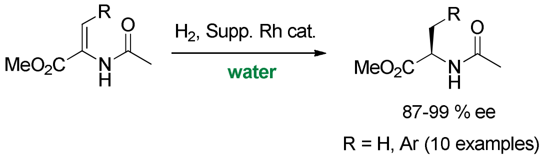

Chiral Rh phosphine-phosphite catalysts immobilized on ionic resins for the enantioselective hydrogenation of olefins in water

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Rh phosphine-phosphite chiral catalysts immobilized on ion exchange resins provides highly enantioselective hydrogenation of enamides in water.