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Authors: Felix Angel Jalon, Margarita Ruiz-Castañeda, M. Carmen Carrión, Lucía Santos, Blanca R. Manzano, and Gustavo Espino

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A Biphasic Medium slows down the Transfer Hydrogenation and allows a Selective Catalytic Deuterium Labeling of Amines from Imines mediated by a Ru-H/D$^+$ Exchange in D_2O.

Margarita Ruiz-Castañeda,[a] M. Carmen Carrión,[a] Lucía Santos [a] Blanca R. Manzano,[a] Gustavo Espino,*,[b] Félix A. Jalón*,[a]

Dedicated to Professor Pascual Royo (in memoriam)

The transfer hydrogenation (TH) of several aldimines has been studied using [RuCl(*p*-cymene)(dmbpy)]BF_4, **1**, (dmbpy = 4,4'-dimethyl-2,2'-bipyridine) as a precatalyst. Both neat water and a biphasic water/toluene mixture (w/t) have been successfully used as solvents. In the w/t medium the corresponding precursors, amine and aldehyde, were also used as substrates for a transfer hydrogenative reductive amination. Selective deuterium labeling of the resulting alkylated amines was the main goal of this work. On using D_2O the D-content in the amine was negligible but a high level of D-incorporation was achieved in D_2O/toluene. According to calculations, this is due to the effect of the relative rates of the hydride transfer and that of the RuH/D$^+$ exchange. The incorporation of deuterium increases with time as a consequence of the reduction in the hydride transfer rate as the substrate concentration diminishes. The recyclability assays performed reflect the importance of pH in the selectivity of the TH towards the imine or the aldehyde resulting from imine hydrolysis.

Introduction

Deuterium-labeled compounds are valuable chemicals that very often are obtained by non-selective and/or energetically exigent methods with expensive or non-ecofriendly deuterium sources[1] such as, for example, $NaBD_4$ [2] or $LiAlD_4$ [3] that are used in stoichiometric amounts. However, deuterated substrates are required for the determination of structures[4] and reaction pathways,[5] as stable isotope tracers,[6] as stable isotopically labeled internal standards in mass spectrometry,[7] for the synthesis of drug compounds with improved metabolic stability,[8] and to provide enhanced contrast in neutron scattering studies.[9] The approaches established for deuterium labeling can be extrapolated to tritium to give a new range of applications.[10]

In addition to the above, as consequence of the increasing demand for environmentally friendly methods in chemistry, the use of water as an alternative solvent in complex-catalyzed reactions is of great interest due to its safety, non-toxicity, simpler product separation and the possibility of catalyst recycling.[11] Another important factor is that D_2O is currently one of the cheapest sources of deuterium.

Amines are desirable organic compounds in a range of applied fields such as medicine, agrochemistry and materials chemistry.[12] Homogeneous transition metal catalysts are commonly used for the deuteration of amines by H/D exchange via C–H bond activation,[13] even in D_2O,[14] although this usually requires harsh conditions and a low level of selectivity is generally achieved.[15] A potential way to obtain deuterated amines is the transfer hydrogenation (TH) of imines[16] or the transfer hydrogenative reductive amination of aldehydes or ketones, both in D_2O. In the reductive amination the amine and aldehyde precursors of an imine are used as starting materials.[17] However, the TH or reductive amination approaches do suffer from some drawbacks such as the scarce incorporation of deuterium (*vide infra*).

Metal-catalyzed hydrogenations in water, including transfer hydrogenation (TH) processes,[18] have been reported in recent years.[19] However, when these reactions are carried out in a single phase, they generally require functionalized catalysts to facilitate their solubility in water[20] or the use of phase transfer catalyst under biphasic conditions.[21] In addition to the problems

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[a] *M. Ruiz-Castañeda, Dr. M. C. Carrión, Dr. L. Santos, Prof. Dr. B. R. Manzano, Prof. Dr. F. A. Jalón*
University of Castilla-La Mancha,
Facultad de Ciencias y Tecnologías Químicas-IRICA,
Avda. C. J. Cela, 10, 13071, Ciudad Real, Spain.
E-mail: Felix.Jalon@uclm.es

[b] *Dr. Gustavo Espino*
University of Burgos,
Departamento de Química, Facultad de Ciencias,
Plaza Misael Bañuelos s/n, 09111, Burgos, Spain.

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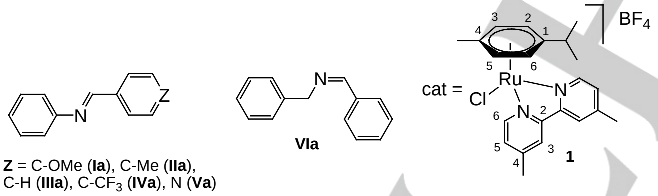
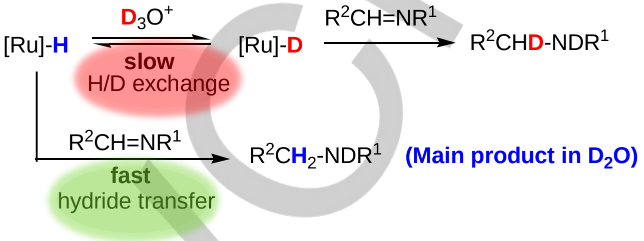
outlined above, the low solubility of molecular hydrogen and the easy hydrolysis of imines are additional limitations. The former problem can be circumvented by using transfer hydrogenation (TH) agents such as the systems HCOOH/HCOONa or $HCOOH/HCOONH_4$.[22] The ready hydrolysis of imines in water or alcohols led to the opinion that they are not suitable substrates for protic solvents.[23] However, Wu et al. successfully investigated the asymmetric TH of aromatic cyclic imines and iminiums salts catalyzed by a water-soluble catalyst in water. A metallacycle system of Ir has been reported by Xiao et al. as active in the hydrogenation of imines in methanol.[24]

In the work described here we aimed to obtain deuterated amines by TH (or by reductive amination) of the aldimines **Ia**–**VIa** depicted in Scheme 1 using catalyst **1** in biphasic D_2O/toluene media and with HCOOH/HCOONa as the hydrogen source. The incorporation of deuterium will be the result of a metal-H/D^+ exchange with acidic D_2O, provided that the deuteron will undergo an inversion of polarity (umpolung). This route has barely been explored for unsaturated substrates[25] and, to the best of our knowledge, this methodology has never previously led to the incorporation of deuterium in amines. It has been reported that the main problem associated with deuterium incorporation in unsaturated substrates is the control of the hydride transfer rate, which must not exceed that of the metal-hydride/D^+ exchange.[26]



Scheme 1.

This statement inspired this work, since in a previous publication[27] we reported the TH of *N*-benzylideneaniline with good TON and TOF values in neat water using **1** as a precatalyst and HCOOH/HCOONa as the hydrogen source. However, our catalytic conditions led to a low level of deuterium incorporation in the α-position of the resulting alkylated amine on using D_2O as the deuterating agent. This fact contrasted with the TH of ketones, such as cyclohexanone, which led to cyclohexanol with a deuterium incorporation in the α-position of over 90%. In accordance with the experimental observations, the results of computational calculations indicated that the Ru-H/D^+ interchange has a slower rate than that of the hydride transfer to *N*-benzylideneaniline and comparable to the hydride transfer to cyclohexanone. This fact could explain the incorporation of deuterium into cyclohexanol but a low deuteration level into the amine (see Scheme 2).



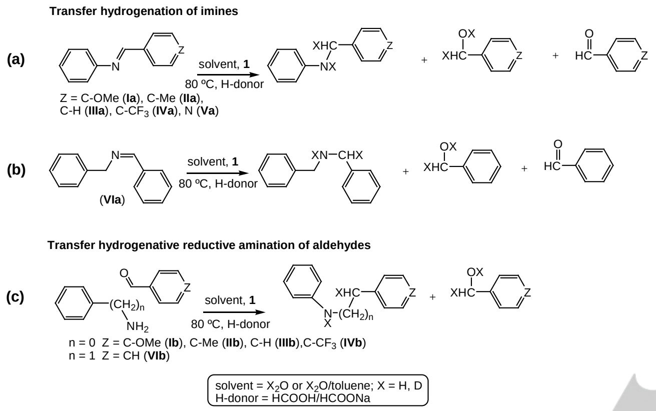
Scheme 2. Scarce deuterium incorporation in the methylene position of the amine in neat D_2O due to the fast hydride transfer.

Considering these ideas, we decided to attempt to slow down the TH rate by using toluene as a second phase (w/t biphasic media) in the absence of a phase-transfer catalyst, which could accelerate the TH process. We have previously demonstrated that the precatalyst and its derivatives are soluble in water at 80 ºC but practically insoluble in toluene, while the imine and amine derivatives are mainly soluble in toluene. In this way, key steps such as the decarboxylation of the formate anion and the Ru-H/D^+ exchange could operate similarly in water and the presence of toluene will not hamper them. However, the rate of hydride transfer to the substrate should be decreased in this medium since the substrate is mainly present in the organic phase. We aimed to show that the use of this strategy would lead to a high level of deuterium incorporation in the resulting amines and that it is a concept that could be applicable to the preparation of labeled (deuterium or tritium) organic substrates.

Results and Discussion

Catalytic TH of imines in water versus water/toluene. In order to demonstrate the ability of our precatalyst **1** to hydrogenate *N*-benzylideneanilines in neat water, experiments were carried out with four differently substituted *para*-*N*-benzylideneanilines. The results and conditions are provided in Table S2. A starting pH of 4.4 was chosen considering the results of our previous work.[27] Besides the expected alkylated amine, variable amounts of *para*-substituted benzaldehyde (resulting from hydrolysis of the substrates) and of *para*-substituted benzylalcohols (resulting from hydrogenation of the aldehydes) were also obtained (see Scheme

3a). The highest yield of the alkylated amine was obtained for the unsubstituted substrate **IIIa** (77% after two hours, TOF = 308). The yield of the other three amines reflects the following favorable effect of the substituent in the *para* position of the benzylidene group: H > Me > CF_3 > OMe. The imine with the CF_3 group is probably less reactive due to a lower polarity of the –N=C– bond.[28] The explanation for the low yield of alkylated amine in the case of OMe seems to be related to the degree of hydrolysis (39% of aldehyde at 7 hours).



Scheme 3.

Our aim was to increase the incorporation of deuterium in the amines applying the strategy outlined in the introduction. As a consequence, it was decided to demonstrate that the TH of imines was also possible in a water/toluene biphasic medium (w/t) but was slowed down with respect to the rate in neat water. The general experimental conditions used in the catalytic assays in w/t medium are indicated in Scheme 3.

Entries 1–28 in Table 1 concern the results obtained for the TH of the *N*-benzylidenealdimines **Ia**–**IVa**, previously tested in water, as well as the reductive amination of their precursors (substituted benzaldehyde + aniline, **Ib**–**IVb**). Entries 29–30, 31 and 32-33 concern substrates **VIa**, **VIb** and **Va**, respectively.

The cat/S/HCOONa ratio of 1/200/6000 was considered to be suitable in a previous study.[27] Experiments in which the cat/substrate/formate ratio was varied did not give better results (compare entries 1 with 2 or 3).

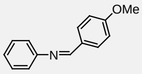
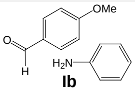
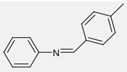
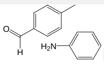
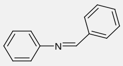
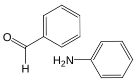
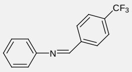
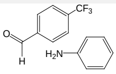
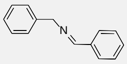
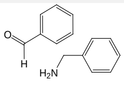
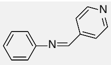
For the *N*-benzylidenealdimines, with the exception of **IVa** where the *para* substituent is the electron-acceptor CF_3 group, the yields of the alkylated amine were around 72–86% in 24 hours (58% for **IVa**) and a negligible increase was observed after a further 24 hours (cf. entries 5 *vs* 6 and 25 *vs* 26). Considering the yield of the amine product at 7 hours as indicative (2 hours in the case of the unsubstituted and more reactive **IIIa**), the expected decrease in the rate of TH when the reaction was carried out in the w/t biphasic medium was observed for aldimines **IIa**–**IVa** (entries 10, 14 and 24). A homogeneous pattern was not observed for the hydrolysis (sum of alcohol and aldehyde): for **IIa** and **IIIa** there were no clear differences between the two media while in the case of **IVa** a higher level of hydrolysis was unexpectedly observed in the biphasic medium. The behavior of substrate **Ia** with OMe was different as it showed an increase in the TH rate in w/t media (entry 4, Table 1) with a noticeable amount of alkylated amine at this time of 72% (34% in water). The observed partial inhibition of the imine hydrolysis (39% in w and 10% in w/t) probably explains this apparent discrepancy, suggesting a possible competition between the two processe~~s~~. This competition can be extended to the benzylamine derivative **VIa**, for which the alcohol produced reached high levels (see entries 29–30) with a low yield of the alkylated amine (33% at 7 hours). The case of imine **Va**, with a 4-pyridyl fragment, is different and reflects a low reactivity: hydrolysis did not take place and, although the alkylated amine was the only product (entries 32–33), the conversion was rather low (31% in 48 h).

According to the information in Table 1 for the aniline derivatives (**I**–**IV**), similar production of the final alkylated amine and also a similar degree of hydrolysis were obtained on starting from the imine or its corresponding aldehyde and aniline precursors (Scheme 3c, cf. entries 5 *vs* 8, 11 *vs* 13, 17 *vs* 22 and 25 *vs* 28 in Table 1, for example). However, in the case of the benzylamine derivative (**VI**) it was advantageous to start from the precursors (entries 29 *vs* 31).

It is interesting to analyze the data obtained after short reaction times in the case of **IIIb** (entries 18 and 19). After 2 and 4 hours there were 17% and 2% of aldehyde present, respectively, while the corresponding alcohol was not detected. This finding indicates that at such short times the aldehyde had not been hydrogenated. The amount of alkylated amine increased from 24% to 63% on going from 2 to 4 hours. This indicates that the imine was hydrogenated selectively over the aldehyde and that the aldehyde reacted with aniline to give the imine as its concentration is reduced with time.

Selective deuterium labeling of amines by TH of imines in D_2O/toluene (dw/t). Once it had been verified that the TH of imines in the biphasic medium was possible, and took place at

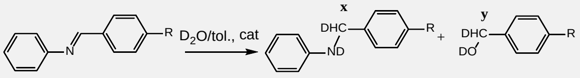
Table 1. Catalytic transfer hydrogenation results for different substrates using **1** in biphasic medium (water/toluene).[a]

Entry	Substrate	Time (h)	Alkylated amine (%) [b]	Alcohol (%)	Aldehyde (%)	Imine (%)
1	 **Ia**	2	20	3	7	70
2		2[c]	31	16	6	47
3		2[d]	12	1	11	76
4		7	72(34)	8	2	18
5		24	84	14	-	2
6		48	88	12	-	-
7	 **Ib**	7	77	3	2	18
8		24	85	15	-	-
9	 **IIa**	2	16	5	4	75
10		7	59(76)	10	7	24
11		24	72	28	-	-
12	 **IIb**	7	56	12	9	24
13		24	80	20	-	-
14	 **IIIa**	2	23(77)	3	13	61
15		7	79	11	2	8
16		14	84	16	-	-
17		24	86	14	-	-
18	 **IIIb**	2	24	-	17	59
19		4	63	-	2	35
20		7	80	7	5	8
21		14	89	11	-	-
22		24	89	11	-	-
23	 **IVa**	2	19	8	4	69
24		7	49(66)	29	1	21
25		24	58	40	-	2
26		48	58	42	-	-
27	 **IVb**	7	49	32	1	18
28		24	62	38	-	-
29	 **VIa**	7	33	58	7	2
30		24	31	65	-	4
31	 **VIb**	7	50	43	5	2
32	 **Va**	24	23	-	-	77
33		48	31	-	-	69

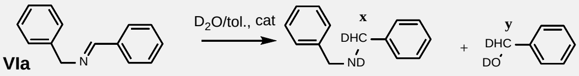
[a] Experiments were repeated at least twice to corroborate reproducibility. T = 80 °C, unless otherwise stated, cat/S/HCOONa = 1/200/6000, cat = 0.64 μmols, cat = 0.5 mol%. Biphasic conditions (2 mL H_2O:1 mL toluene), initial pH = 4.4 adjusted with HCOOH, 500 rpm. [b] Values in parenthesis correspond to the processes in neat water. [c] Experiment with cat/S/HCOONa = 2/200/6000, cat = 1.252 μmols. [d] Experiment with cat/S/HCOONa = 1/400/6000, cat = 0.626 μmols. Conversions were determined by ^{1}H NMR spectroscopy.

a lower rate than in water (with the apparent exception of **Ia**), we evaluated whether this could lead to a higher level of selective deuterium incorporation in the resulting amine on using D_2O as the deuterium source. A reaction time of 24 hours was selected since at this time a high yield of amine was obtained (Table 2). Substrate **Va** was excluded from the study due to the ineffective TH.

Table 2. Deuterium labeling of alkylated amines using **1** in D_2O/toluene (dw/t) by TH of imines.[a]



R = OMe (**Ia**), Me (**IIa**), H (**IIIa**), CF_3 (**IVa**)

Entry	Subs.	Time (h)	Alkyl. amine (%)	x (%)	Alcohol (%)	y (%)	Amine/ Alcohol ratio	Imine (%)
1	**Ia**	24	82	87	18	89	4.5	2
2	**Ia**	24[b]	89	7	11	80	8.1	--
3	**Ia**	48	84	91	21	97	4.0	--
4	**Ib**	24	89	38	11	89	8.1	--
5	**IIa**	24	80	78	20	70	4.0	--
6	**IIb**	24	86	62	14	90	6.1	--
7	**IIb**	24[b]	87	5	8	74	10.9	5
8	**IIIa**	24	88	93	12	92	7.3	--
9	**IIIa**	48	90	91	10	96	9.0	--
10	**IIIb**	24	91	38	8	89	11.4	1
11	**IIIb**	24[c]	90	48	10	86	9.0	--
12	**IVa**	24	77	51	23	33	3.3	--
13	**IVb**	24	73	51	27	37	2.7	--
	VIa 							
14	**VIa**	24	40	76	59	72	0.8	1
15	**VIb**	24	46	74	50	70	0.9	4

[a] Experiments were repeated at least twice to corroborate reproducibility. T = 80 °C. Unless otherwise stated, cat/S/HCOONa = 1/200/6000, cat = 0.626 μmols, cat = 0.5 mol%., biphasic conditions (2 mL D_2O:1 mL toluene), initial pD = 4.8 adjusted with HCOOH, 500 rpm; x and y are the % of deuterium incorporation in the alfa-position of the alkylated amine or the alcohol respectively. [b] Monophasic condition (2 mL D_2O) maintaining the rest of conditions. [c] cat/S/HCOONa = 1/100/6000, cat = 1 mol%., rest of the conditions as in [a]. Conversion was determined by ^{1}H NMR spectroscopy.

To our delight, a high level of deuterium incorporation in the α-alkyl position of the amine was generally obtained (x%) and variable amounts of the alcohol deuterated in the α position (y%) were also obtained (Table 2).

Deuterium incorporation was markedly higher than the negligible amounts obtained in neat D_2O (entries 1 *vs* 2 and 6

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vs 7). As one would expect,[25][29] in the alcohols obtained from the respective aldehyde, the deuterium was incorporated at an excellent level in both media. When the deuterium levels of the resulting alkyl amines were compared, a dependence of the deuterium incorporation with the substrate was observed. While the unsubstituted benzylaniline and that with the OMe substituent reached levels of around 90%, the amine with a Me substituent and the dibenzylamine led to values in the range 76–78%. The alkyl amine that exhibited the lowest incorporation was the benzylaniline with the CF_3 substituent, for which the incorporation was only 51%.

From the point of view of deuterium incorporation (x%), the use of the imine as the substrate was clearly advantageous when compared to the use of a mixture of their precursors amine and alcohol (entries 1 *vs* 4, 5 *vs* 6 and 8 *vs* 10) with the exception of the easily hydrolyzed imines (entries 12 *vs* 13 and 14 *vs* 15), which gave similar results.

A control experiment, in the absence of catalyst, was carried out, consisting in the use of the imine **IIIa** (Fig. S1) in the standard catalytic conditions. Only non-deuterated **IIIa** and the corresponding benzaldehyde (18%, consequence of hydrolysis) were obtained. This experiment indicates that the TH is not operative without catalyst and that the deuterium incorporation is a catalytic process as well. Also experiments with *N*-benzylphenylamine or benzyl alcohol were performed in the presence of **1** in D_2O/toluene and no deuterium incorporation was observed (Fig. S2 and S3) indicating that the D-incorporation takes place in the TH process.

It was decided to study the evolution with time of the D incorporation both in the amine and in the alcohol. This study was carried out with the pair aniline-benzaldehyde (**IIIb**) in the biphasic medium dw/t (see Figure 1). After 24 hours a high yield of alkylated amine (91%) with a low level of D incorporation (38%) and 9% of alcohol with 89% D incorporation were obtained. The aim was to evaluate if the high rate of the reductive amination was associated with a low D content in the alkylated amine. After short reaction times (2–7 h) the percentage of deuterium incorporation in the amine was low and this increased with time until a stable level of around 40% was reached after longer times (14–24 h). A similar evolution was observed for the alcohol but higher levels of D incorporation were observed from the beginning.

All of these observations could be a consequence of the different rates of the hydride transfer of imines and aldehydes, on the one hand, and of the RuH/D$^+$ exchange, on the other. It has previously been stated that imines are more easily hydrogenated than aldehydes in acidic media ($k_{\text{Hyd.T. imine}} > k_{\text{Hyd.T. aldehyde}}$, Hyd.T. = hydride transfer).[27] The low D content in the alkylated amine must be an indication of the following order in rate constants: $k_{\text{Hyd.T imine}} > k_{\text{RuH/D}^{+}\text{exchange}}$ and the deuterium incorporation increases when the concentration of the imine is low enough to slow down the rate of hydride transfer process, a situation that occurs after long reaction times. In the case of the aldehyde, the similar rates of hydride transfer and RuH/D$^+$ exchange allowed D incorporation from the beginning but, in any case, a decrease in the concentration of aldehyde favored deuteration of the alcohol. To support this hypothesis the correlation of the deuterium incorporation *vs* the remaining substrate (imine **Ia** or the corresponding aldehyde) with time was analyzed (see Figure 2). According to the symmetric evolution of these plots, it is clear that the lower the amount of substrate that remains the higher the deuterium incorporation.

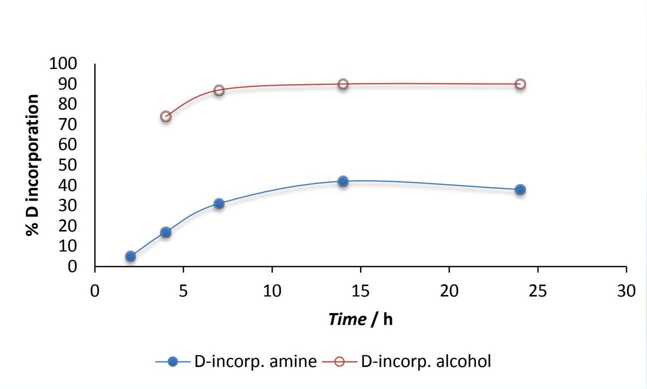

Figure 1. Variation with time of the deuterium incorporation in *N*-benzylideneaniline (—) and benzyl alcohol (—).

In line with this statement, it has been verified that by decreasing the initial concentration of the substrate (entry 10 *vs* entry 11, Table 2), the incorporation of deuterium in the alkyl-amine was increased from 38 to 48%.

In accordance with the interpretation of relative rates, the Gibbs energy barriers for the hydride transfer to the *N*-benzylideneaniline (**IIIa**) and for the RuH/D$^+$ exchange were theoretically calculated[27] in neat water as 2.3 and 12.7 kcal mol^{-1}, respectively (Figure 3).

In this work we calculated that the Gibbs energy barrier for the hydride transfer to the benzaldehyde is 8.2 kcal mol^{-1}. As stated above, in the w/t medium the hydride transfer processes slow down and the barriers should be higher.

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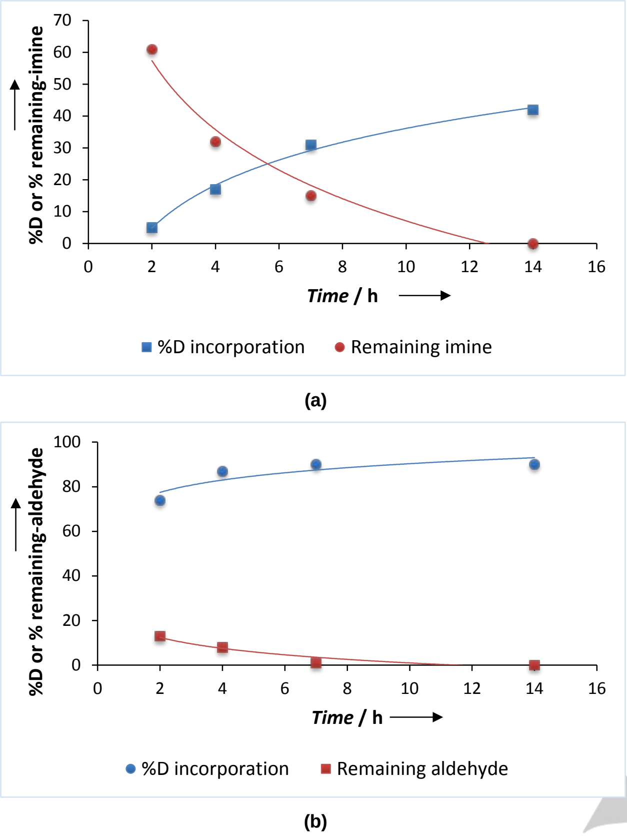

Figure 2. Graphical correlation between the percentage of deuterium incorporation in the substrate and that of the remaining substrate with time. (a) Imine **Ia** to alkylated amine (b) Aldehyde in **Ib** to alcohol.

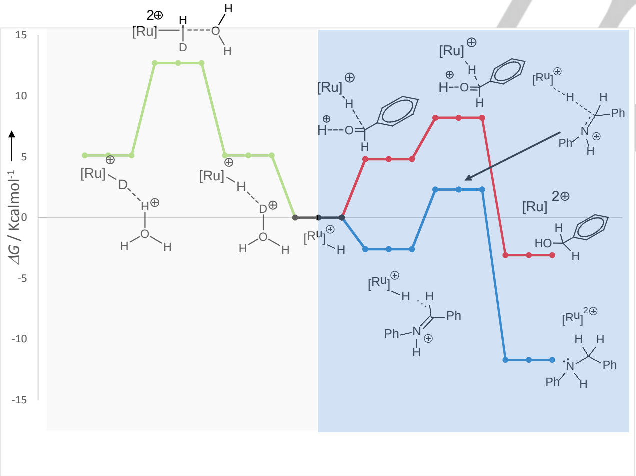

Figure 3. Reaction coordinate for the hydride transfer on the *N*-benzylideneaniline (—) or benzaldehyde (—) and for the Ru-H/D$^+$ exchange in **1** (—). Some data are taken from ref 27.

Aniline and benzaldehyde (**IIIb**) were chosen as substrates for a comparative study of the progression of the different species in w/t and in dw/t. It was found that the kinetic evolution of the species (imine, alkylated amine, alcohol and aldehyde) was very similar in w/t and in dw/t (see Figure S5), a fact that indicates the absence of a significant isotopic effect with this substrate.

Catalytic recycling trials. Catalyst recycling experiments were carried out with equimolar amounts of aniline and benzaldehyde (**IIIb**) as substrates, in the w/t biphasic medium, at the standard described catalytic conditions for four cycles of 24 hours each. Two recycling experiments were performed with and without the addition of formic acid at the beginning of each new cycle and the results were clearly different (see Figure 4). When formic acid was not added (Figure 4a) the formation of the alkylated amine decreased markedly in the second cycle (55%) and it was only 5% in the next two cycles. This decrease in the yield of alkylated amine is not related to the loss of catalytic activity, since in fact benzaldehyde is reduced to the corresponding alcohol with a high yield. This result can be interpreted in terms on the effect that the pH has on the selectivity of the catalyst. The initial pH was 4.4 but it was 8 at the end of the fourth cycle as a consequence of the consumption of formic acid in the TH process. The catalyst is therefore very active towards the hydrogenation of the imine in the first cycle at the initial pH but, according to the data, it is increasingly selective towards the TH of the benzaldehyde when the number of cycles and the pH have increased. It is known that the protonation is an essential requirement for an efficient TH in imines[30] but this is not the case for aldehydes.[31] The small amount of remaining imine in cycles 3 and 4 is probably a consequence of the extensive hydrogenation of the aldehyde, which in turn promotes the hydrolysis of the imine.

In an attempt to overcome these problems fresh formic acid was also added at the beginning of each cycle (see Figure 4b). The optimum amount of formic acid was estimated to be that consumed in the TH of each cycle, which means an equimolar amount with respect to the added substrate (assuming 100% conversion). Conversion to the amine was clearly improved. However, a progressive increase in the amount of unreacted imine and alcohol was observed with the number of cycles. Aldehyde was not observed in any cycle.

Proposed mechanism for the imine TH. Before proposing a catalytic cycle, we tried to detect some of the intermediates. An experiment consisting on the addition of 10 eq. of HCOONa over a D_2O solution (0.5 mL) of precatalyst **1** at r.t. in an NMR tube was performed (see Figure S6). Interestingly, the chlorido-, aquo- and formato-complexes were detected in the ^1H NMR

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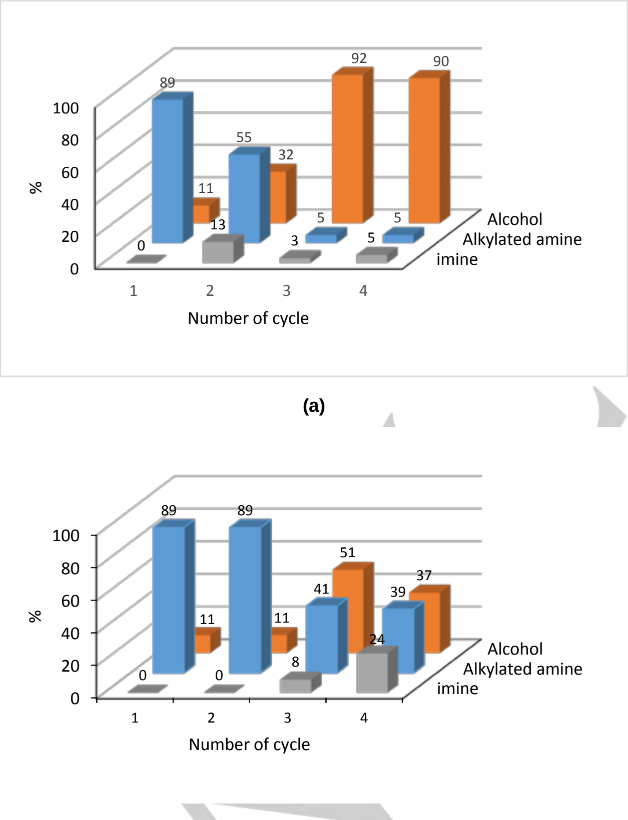
spectrum (the aqua-complex could be detected as a single species in solution by the reaction of the chloride-complex with a slight excess of $AgBF_4$, see experimental section). In addition, a new species appeared slowly which was assigned to the hydrido-complex, although the resonance of the Ru-H group was absent. However, the corresponding Ru-D resonance was detected in the ^2H NMR spectrum (Fig. S9). To ensure that this new species was the hydrido-complex, H_2O (0.2 mL) was added to the solution. A new resonance at - 6.3 ppm appeared immediately in the ^1H NMR spectrum (Fig. 8c) reflecting a Ru-H ↔ Ru-D exchange. The proposed catalytic cycle (Figure 5) for the hydrogenation of imines is based on these findings and on the theoretical calculations performed in our previous work.[27] The hydrido-complex (iv) that can be considered the key form in the catalytic cycle and is formed by decarboxylation of the formato species. The aforementioned Ru-H ↔ Ru-D exchange must take place through a dicationic dihydrogen ([Ru](HD)) compound (v) formed by the reaction of the hydride with D^+ although this species has not been identified.



(a)

(b)

Figure 4. Recycling experiments for the TH of benzaldehyde + aniline (**IIIb**) in a biphasic w/t medium without (a) and with (b) the addition of 4.9 µL of formic acid at the beginning of each cycle. See discussion for further details

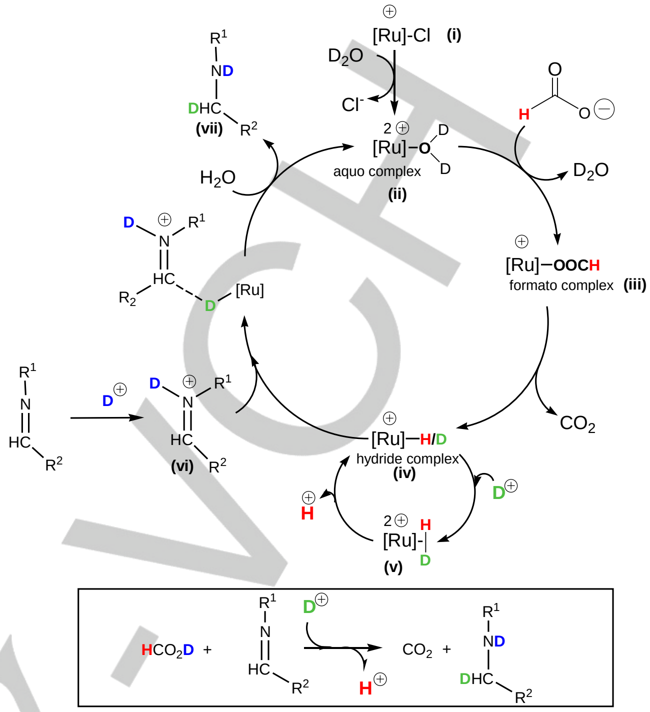


Figure 5. Proposed mechanism for the hydrogenation of imines in an acidic D_2O media.

This species must be acidic enough to liberate H^+. In this way, the incoming D^+ is transformed into a Ru-D(δ^-) group that is transferred to the substrate. Such a change of polarity of the D^+ is named an “umpolung” process.[29b] The hydride transfer to the imine is a process that takes place easily but needs the prior protonation of this substrate, which is transformed into an iminium salt (vi). This transfer can be of a deuteride if the umpolung process is fast enough. The resulting alkylated amine (vii) is liberated to the medium and substituted by a water molecule and the cycle starts again. The limiting step is the decarboxylation of the formate anion.[27] The total catalytic process is included in the lower part of Figure 5 and it involves the transfer of a hydride (or deuteride if the umpolung is operating) and a deuteron from an HCOOD molecule to the imine, which is transformed into the alkylated amine and a molecule of CO_2 is released. According to this cycle and the overall reaction, the pH must be decisive in the hydride transfer step due to the necessary imine protonation and since a formic acid is consumed in the formation of the alkylated amine. Besides, the acid pH is also important in the umpolung process where a deuteron is also necessary. The TH process of the aldehydes can procced in a similar way, with the difference that the protonation of the substrate is not a necessary step.[31]

Besides, a deuteration experiment of *N*-benzylideneaniline under standard conditions (those indicated as [a] in the footnotes of Table 2) in dw/t was carried out and the absence of ***D***COOD in the aqueous phase was verified (Fig. S4). This fact allows to discard a process involving deuteration of the formate anion ($DCOO^-$) and a consecutive deuterium transfer to the metal (as an alternative to the umpolung process).

Conclusions

A set of five aldimines of the type *para*-substituted *N*-benzylideneaniline and *N*-benzylidenebenzylamine have been successfully hydrogenated by a TH process using buffered HCOONa/HCOOH solutions, as the hydrogen source, in neat water or a water/toluene biphasic medium. The conversion of substrates is not related to an electronic effect of the substituents in the *para* position of the benzaldehydes used. The activity for the formation of the alkylated amines follows the order H > Me > CF_3 while the yield with the substrate containing OMe depends strongly on the solvent medium. Conversions from the imine or from the respective aldehyde and amine precursors (transfer hydrogenative reductive amination) gave similar results

Calculations at the DFT level for the non-substituted *N*-benzylideneaniline show that the hydride transfer to imines and aldehydes in water is faster than the Ru-H/D^+ exchange, and thus any strategy that reduces the rate of hydride transfer may favor the incorporation of deuterium in the final product. In line with this idea, we have experimentally shown that the use of a water/toluene two-phase medium slows down the TH process and makes it feasible to achieve high levels of deuterium incorporation in the α position of the resulting amines. In relation to this effect, it has been shown in one example with using a reductive amination procedure that the degree of incorporation of deuterium increases at long reaction times, when the rate of the reductive amination process is reduced due to the decrease in the substrate concentration. This opens a new strategy, verified with one experiment, for the incorporation of deuterium in amines (or other products) due to a lower initial concentration of the substrate.

The main achievement in this work is the proof of concept that reducing the rate of TH of imines with two different strategies leads to a higher level of deuterium incorporation in the resulting amine. This could open new ways to label a diverse range of substrates with hydrogen isotopes from D_2O or T_2O.

Experimental Section

Experimental Details. All reactions were carried out under an atmosphere of dry oxygen-free nitrogen, using Schlenk-vacuum line techniques. Complex **1** was prepared as previously described.[27] Solvents were distilled from the appropriate drying agents and degassed before use. The HCOONa/HCOOH buffer solution was prepared from HCOONa (6.53 g, 96.0 mmol) and HCOOH (650 µL, 17.2 mmol) in water (HPLC grade). The volume was adjusted to 25 mL in a volumetric flask. The precatalyst solution was prepared by dissolving the precatalyst (8.5 mg of complex **1**, 15.65 µmol) in water (HPLC grade) and adjusting the volume in a 25 mL volumetric flask. Once the solutions had been prepared, nitrogen was bubbled through for several minutes and they were stored under an inert atmosphere.

General synthesis of imines used as substrates in the catalytic process. In the synthesis of the imines the starting materials were aniline or benzylamine and the corresponding aldehyde, with the exception of the *N*-benzylideneaniline, which was used as a commercial product. All these reactive were obtained from Aldrich and used in commercial degree.

To a round-bottomed flask the corresponding aldehyde (5.12 mmol) and aniline (467.1 µL, 5.11 mmol) or benzylamine (712.5 µL, 6.52 mmol) were added. Vacuum cycles were performed in order to remove the water produced in the reaction. The mixture was left overnight without stirring at room temperature. The products were purified by recrystallization from methanol. The solids were dried under vacuum. In all cases a yellow solid was obtained in high yield (84–99%). ^1H and $^{13}C\{^1H\}$-NMR spectra were consistent with data from the bibliography.[32]

General procedure for catalytic hydrogenation of imines in biphasic medium. For the catalytic runs, a Teflon®-capped 10 mL ampoule sealed with a Young valve was charged with 1 mL of the buffer solution (HCOONa/ HCOOH) and 1 mL of the catalyst solution, with 0.128 mmol of different substrates (27 mg of *N*-(4-methoxybenzylidene)aniline, 25 mg of *N*-(4-methylbenzylidene)aniline, 23.2 mg of *N*-benzylideneaniline and 31.9 mg of *N*-(4-trifluoromethylbenzylidene)aniline) dissolved in 1 mL of toluene. Nitrogen was bubbled through the mixture for several minutes. The cat/substrate/HCOONa ratio was 0.64 µmol/0.128 mmol/3.84 mmol = 1/200/6000, and the precatalyst concentration was 0.32 mM. For each experiment, two ampoules with identical concentrations were introduced simultaneously into a homemade multi-hole reactor preheated at 80 °C (mineral oil bath and temperature sensor control), and the mixtures were magnetically stirred for the corresponding reaction time. The ampoules were then cooled in an ice/water bath and the solutions were transferred to a 5 mL vial and kept refrigerated until analysis. The toluene phase was separated from the aqueous phase. The resulting aqueous phase was extracted with diethyl ether (2 × 5 mL). The organic phases were combined and then evaporated in air. Samples were placed in an NMR tube containing $CDCl_3$ (0.5 mL) and the signals were referenced to TMS. Conversion and yields were determined by integration of the ^1H NMR spectra.

General procedure for catalytic hydrogenation of imines in monophasic medium. In this case, the same procedure as described previously was followed but without adding toluene. Different substrates were charged into the ampoule directly and the same cat/substrate/HCOONa ratio was used. The resulting aqueous phase was extracted with diethyl ether (2 × 5 mL). The organic phases were combined and then evaporated in air. Samples were placed in an NMR tube containing $CDCl_3$ (0.5 mL) and the signals were referenced to TMS. Conversion and yields were determined by ^1H NMR spectroscopy.

General procedure for catalytic reductive amination of carbonyl compounds with amines in biphasic medium. For the catalytic runs, a 10 mL ampoule sealed with a Young valve was charged with 1 mL of the buffer solution (HCOONa/HCOOH) and 1 mL of the catalyst solution, with 0.128 mmol of amine dissolved in 1 mL of toluene (11.67 µL of aniline) and 0.128 mmol of different substrates (15.54 µL of 4-methoxybenzaldehyde, 13.01 µL of benzaldehyde, 17.55 µL of 4-trifluoromethylbenzaldehyde, 15.15 µL of 4-methylbenzaldehyde) were added.

Selective deuteration experiments. The buffer and precatalyst solutions were both prepared in D_2O (instead of H_2O) in the same way as described previously. It is noteworthy that other reagents (HCOONa, HCOOH and toluene) were not deuterated. For the catalytic runs, the same procedure as described above was followed.

Catalyst recycling with addition of HCOOH. This study was carried out using benzaldehyde and aniline as substrates. All of the procedures were performed under an inert atmosphere. After the first catalytic cycle, following the same procedure as described above at 80 °C for 24 h, the reaction was stopped in an ice/water bath. Once the solution was at room temperature, the organic phase was separated. The resulting aqueous phase was extracted by adding diethyl ether (2 × 5 mL). For this extraction, the mixture was vigorously stirred for several minutes, left to stand, and decanted into the ampoule. Pasteur pipettes were used to separate the organic phases. The yield was calculated from the ^1H NMR spectrum in $CDCl_3$. Fresh benzaldehyde, aniline, toluene and HCOOH (4.8 µL, 0.128 mmol) were then added to the aqueous phase and a new cycle was run. A total of four cycles were studied.

Catalysis recycling without addition of HCOOH. In this case, the experiment was carried out as described above without the addition of HCOOH at the end of each cycle. A total of four cycles were studied.

Detection in solution of [(*p*-cymene)Ru(OD$_2$)(dmbpy)]$^+$. In a light-preserved NMR tube, containing [(*p*-cymene)RuCl(dmbpy)]BF_4 (**1**) (5 mg, $9.22 \cdot 10^{-3}$ mmol) in 0.5 mL of D_2O, 1.2 equivalents of $AgBF_4$ (2.2 mg, $11.3 \cdot 10^{-3}$ mmol) were added. ^1H RMN (300 MHz, D_2O, 298K, see Scheme 1 for numbering): δ = 0.80 (d, J = 7.68 Hz, 6H, Me_{iPr}(p-cym)); 2.09 (s, 3H, Me_{Tol} (p-cym)); 2.34 (sept, 1H, CH_{iPr} (p-cym)); 2.47 (s, 6H, Me (bpy)); 5.87 (d, J = 6.5 Hz, 2H, $H^{3/5}$ (p-cym)); 6.10 (d, J = 6.5 Hz, 2H, $H^{2/6}$ (p-cym)); 7.52 (d, J = 5.8 Hz, 2H, H^5(bpy)); 8.10 (s, 2H, H^3 (bpy)); 9.26 (d, J = 5.8 Hz, 2H, H^6(bpy)), ppm. $^{13}C\{^1H\}$-RMN (125 MHz, D_2O) δ = 20.56 (Me_{Tol}); 23.52 (Me_{bpy}); 23.89 (Me_{iPr}); 33.15 (CH_{iPr}); 85.89 ($C_{3/5}$(p-cym)); 90.18 ($C_{2/6}$(p-cym)); 102.62 (C_1/C_4(p-cym)); 107.61 (C_1/C_4(p-cym)); 127.68 (C_3(bpy)); 131.89 (C_5(bpy)); 157.27 (C_6(bpy)); 157.41 (C_2(bpy)); 157.49 (C_4(bpy)), ppm. Signals were referenced to (4,4-dimethyl-4-silapentane-1-sulfonic acid) (DSS).

Solubility tests. The data are included in the SI.

Computational Details. Calculations were performed at the DFT level using the M06 functional including an ultrafine integration grid, as implemented in Gaussian 09.[33] The Ru atom was described using the scalar-relativistic Stuttgart-Dresden SDD pseudopotential and its associated double-ζ basis set,[34] complemented with a set of *f*-polarization functions.[35] The 6-31G(d,p) basis set was used for the H,[36] C, N, O and Cl atoms.[37] To take into account both nonspecific and specific interactions with the solvent, a mixed continuum/discrete solvent model was used.[38] In this model, in addition to the continuum description of the solvent (SMD continuum model)[39] three explicit water molecules, able to establish hydrogen-bonding interactions with the catalyst and the substrate, have been included. The structures of the reactants, intermediates, transition states and products were optimized in water solvent (ε = 78.35) using this cluster-continuum model. Frequency calculations were carried out for all the optimized geometries to characterize the stationary points (zero imaginary frequency) as either minima or transition states (one imaginary frequency). Intrinsic reaction coordinate (IRC) calculations[40] were computed for the transition states to confirm they connect with the corresponding intermediates. All the energies collected in the text are Gibbs energies in water at 298K.

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Conflict of interest

Authors declare no conflict of interest

Keywords: Ruthenium • Deuterium labeling • Transfer hydrogenation • Reductive amination • Imine

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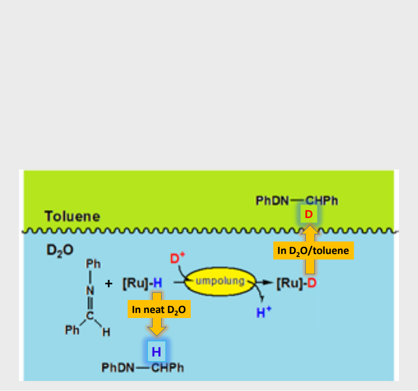

Margarita Ruiz-Castañeda,[a] M. Carmen Carrión,[a] Lucía Santos,[a] Blanca R. Manzano,[a] Gustavo Espino,*,[b] Félix A. Jalón,*[a]

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A Biphasic Medium slows down the Transfer Hydrogenation and allows a Selective Catalytic Deuterium Labeling of Amines from Imines mediated by a Ru-H/D^+ Exchange in D_2O.