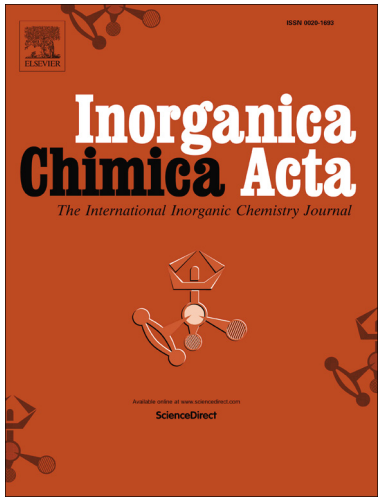


2,2,2-Trifluoroethanol-assisted imine hydrogenation by a Ru-monohydride

Ivan Scodeller, Antonella Salvini, Gabriele Manca, Andrea Ienco, Lapo Luconi, Werner Oberhauser

PII: S0020-1693(15)00143-7
DOI: http://dx.doi.org/10.1016/j.ica.2015.03.009
Reference: ICA 16459

To appear in: *Inorganica Chimica Acta*

Received Date: 14 January 2015
Revised Date: 9 March 2015
Accepted Date: 11 March 2015

Please cite this article as: I. Scodeller, A. Salvini, G. Manca, A. Ienco, L. Luconi, W. Oberhauser, 2,2,2-Trifluoroethanol-assisted imine hydrogenation by a Ru-monohydride, *Inorganica Chimica Acta* (2015), doi: http://dx.doi.org/10.1016/j.ica.2015.03.009

2,2,2-Trifluoroethanol-assisted imine hydrogenation by a Ru-monohydride

Ivan Scodeller [a], Antonella Salvini [a], Gabriele Manca [b], Andrea Ienco [b], Lapo Luconi [b], Werner Oberhauser [b,*]

[a] *Dipartimento di Chimica "Ugo Schiff", Università di Firenze, via della Lastruccia 3-13, 50019 Sesto Fiorentino, Italy*

[b] *Istituto di Chimica dei Composti Organometallici (CNR-ICCOM), Area di Ricerca CNR di Firenze, via Madonna del Piano 10, 50019 Sesto Fiorentino, Italy*

Corresponding author. Tel.: +39-055-5225284; Fax: +39-055-5225203

E-mail address: werner.oberhauser@iccom.cnr.it (W. Oberhauser)

ABSTRACT

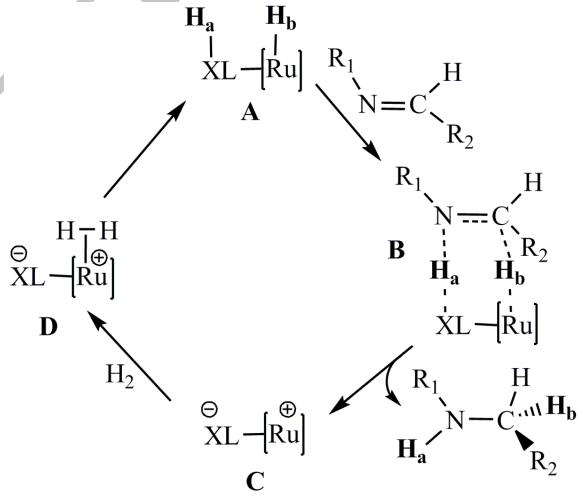
The *trans* heterodiphosphane Ru-based compound of the formula $[Ru(OAc)_2(CO)_2(P^nBu_3)(PPh_3)]$ proved to be a suitable precatalyst for imine hydrogenation in 2,2,2-trifluoroethanol (TFE) without the addition of an external base. High-pressure (HP) NMR investigations combined with a DFT-study, carried out on a related model precatalyst, were indicating the formation of a cationic Ru-monohydride-2,2,2-trifluoroethanol (TFE) species that catalyzes the imine hydrogenation by a TFE-assisted outer-sphere reaction mechanism.

Keywords: Imine hydrogenation; Ruthenium; 2,2,2-Trifluoroethanol; High pressure NMR spectroscopy

1. Introduction

Amines are an important class of organic compounds which are applied in the synthesis of a variety of biologically active molecules including natural and synthetic products [1]. The hydrogenation of enamines and imines to amines is mostly catalyzed by well-defined Rh-, Ir- and Ru-based catalysts [1]. Among them, Shvo's dinuclear ruthenium [2] and Noyori's RuCl(*p*-cymene)(N-*p*-toluenesulfonyl-1,2-diphenylethylenediamine) catalyst [3] have been intensively studied from a mechanistic point of view. In this context, inner- versus ligand-assisted outer-sphere mechanisms were discussed to be operative under real catalytic imine hydrogenation conditions [4]. The inner-sphere-based catalytic imine hydrogenation reaction occurs on the Ru(II)-coordinated imine, which implies the formation of a vacant coordination site on the metal centre for substrate coordination.

In contrast, the ligand-assisted outer-sphere reaction mechanism (Scheme 1) involves a metal-monohydride species (A) containing an ancillary ligand with a polar functional group such as OH or NH.



Scheme 1. Ligand-assisted Ru-based imine hydrogenation (LXH = ligand with a polar functional group.

The interaction between the substrate and the hydride species A forms species B (Scheme 1) [4]. H^+ and H^- are transferred to the substrate, either concerted [5] or stepwise (*i.e.* ionic mechanism)

[6], leading to a zwitterionic Ru-species (C) under the concomitant release of the amine product. The catalytic cycle is then closed by a ligand-assisted heterolytic dihydrogen splitting (D) [7], generating the initial Ru(II)-monohydride species. This latter species is mostly generated by the action of an external strong base such as KO^tBu_3 [8]. Hence the presence of an internal base (*i.e.* alkoxy or acetate group) in the precatalyst circumvents the undesired addition of a costly base, which negatively impacts the environment. In this context, we used the Ru bis-acetate complex $[Ru(OAc)_2(CO)_2(P^nBu_3)(PPh_3)]$ (**1**) [9] as precatalyst for the hydrogenation of selected imines to the corresponding amine in different reaction media, obtaining with 2,2,2-trifluoroethanol (TFE) the highest substrate conversion at moderate catalytic reaction conditions (*i.e.* T= 50 °C and $p(H_2)$ = 25 bar).

2. Experimental

2.1. Materials

1 [9], $[Ru(OAc)_2(CO)_2(P^nBu_3)_2]$ (**2**) [10a] and $[Ru(OAc)_2(CO)_2(PPh_3)_2]$ (**3**) [10b] were synthesized according to reported synthesis procedures. N-benzylideneaniline, N-benzylidene-*p*-toluidine, benzaldehyde and *p*-fluoroaniline were purchased from Aldrich and used without further purification. Toluene and THF were purified by distillation over Na/benzophenone, MeOH by distillation over Mg and TFE by distillation over anhydrous potassium carbonate.

2.2. Instrumentation

Operando ^1H and $^{31}P\{^1H\}$ high pressure (HP) NMR spectroscopic experiments were carried out on a Bruker Avance DRX-300 spectrometer operating at 300.13 and 121.98 MHz, respectively, using a 10 mm BB probe and a 10 mm sapphire tube (Saphikon, Milford, NH) equipped with a home-made titanium high pressure charging head [11]. Chemical shifts (δ) are reported in ppm relative to TMS (^1H NMR) or 85% H_3PO_4 ($^{31}P\{^1H\}$ NMR). GC analyses were carried out on a Shimadzu GC 2010 equipped with a Phenomenex Zebron-5HT capillary column (15 m × 0.32 mm

× 0.1 μm) and a flame ionization detector. GC-MS analyses were performed on a Shimadzu QP5000 apparatus, equipped with a 30 m (0.32 mm i.d., 0.50 μm film thickness) CP-WAX 52 CB WCOT-fused silica column. Elemental analysis was carried out with a NA 1500 Carlo Erba elemental analyzer.

2.3. Synthesis of N-benzylidene-p-fluoroaniline

p-Fluoroaniline (1.0 mL, 10.4 mmol) was added to MeOH solution (10.0 mL) of benzaldehyde (0.8 mL, 7.8 mmol) and acetic acid (20 μL, 0.35 mmol). The solution was refluxed for 4 h, followed by its cooling to room temperature. The crystalline product was filtered off, washed with water and then dissolved in ethyl ether (15.0 mL). The organic solution was washed with diluted HCl, then dried over anhydrous Na_2SO_4 and the solvent removed by vacuum distillation giving a slightly yellow crystalline product (1.103 g, 71%). Anal. Calcd for $C_{13}H_{10}FN$ (199.22): C, 78.37; N, 7.03; H, 5.06. Found: C, 78.95; N, 6.89; H, 5.29. ^{1}H NMR (300.13 MHz, $CDCl_3$) δ 7.10 (m, 4H; Ar*H*), 7.48 (m, 3H, Ar*H*), 7.88 (dd, ^3J(HH) = 7.5 Hz, ^4J(HH) = 3.6 Hz, 2H, Ar*H*), 8.45 (s, 1H, C*H*=N).

2.4. Operando (HP) NMR study

Three solutions (2.0 mL) of **1** (14.8 mg, 0.020 mmol) were prepared under a nitrogen atmosphere, using as solvent neat C_6D_6 or two different solvent mixtures (*i.e.* 1:1 (v:v) C_6D_6/MeOH or C_6D_6/TFE). Each solution was then transferred into a 10 mm sapphire tube, which was sealed and introduced into the NMR probe at room temperature. Two additional solutions were prepared in neat C_6D_6 or in a 1:1 (v:v) C_6D_6/TFE solvent mixture with N-benzylideneaniline (0.5 mmol), dissolved together with **1**. After the acquisition of $^{31}P\{^1H\}$ and ^{1}H NMR spectra at room temperature, the sapphire tube was successively removed from the NMR probe, charged with dihydrogen ($p(H_2)$ = 50 bar) and reinserted into the NMR probe, followed by the acquisition of NMR spectra at room temperature. Then the NMR probe was heated to 50 °C (*i.e.* catalytic reaction temperature), followed by the acquisition of NMR spectra in time intervals of 0.5 h up to 1.5 h. The

NMR probe was then allowed to cool to room temperature, the excess dihydrogen gas released and the catalytic solution objected to GC-MS analysis.

2.5. Conversion of $[RuH_2(CO)_2(P^nBu_3)(PPh_3)]$ into $[RuH(OAc)(CO)_2(P^nBu_3)(PPh_3)]$ in the presence of TFE or MeOH. An NMR experiment

A solution of $[RuH_2(CO)_2(P^nBu_3)(PPh_3)]$ (**1(H)$_2$**) (3.6 mM) in C_6D_6 (0.75 mL) was synthesized according to a reported procedure [12], giving the desired product with 84 % yield along with **2** (8%) and $[RuH_2(CO)_2(PPh_3)_2]$ (**3(H)$_2$**) (8%). The latter solution was equally divided in two portions, followed by the addition of TFE (0.4 mL) to one portion and MeOH (0.4 ml) to the other one. Afterwards $^{31}P\{^1H\}$ and ^1H NMR spectra were acquired with both solutions. Acetic acid (HOAc) (2.0 μL) was then added to each solution at room temperature and $^{31}P\{^1H\}$ and ^1H NMR were acquired with both solutions at room temperature in time intervals of 1 h.

2.6. Catalytic imine hydrogenation reactions

In a glass vial placed in a stainless-steel autoclave (150.0 mL), were successively added under a nitrogen atmosphere, the precatalyst (0.005 mmol), substrate (0.5 mmol), solvent (8.0 mL) and *p*-xylene (64.0 μL) as internal standard. Afterwards the autoclave was sealed, charged with dihydrogen, heated in an oil bath and rocked for the desired reaction time, then cooled to room temperature depressurized and the reaction mixture analyzed by GC and GC-MS.

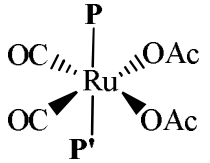
2.7. Computational details

All calculations were performed at B97D-DFT level of theory [13a] within the Gaussian 09 package.[S1] Solvent effects were modeled by using the Conductor Continuum Polarizable Model (CPM) [13b,c] The Stuttgart-Dresden pseudo-potential has been used for ruthenium [13d], while 6-31+G(d,p) for all other atoms with the important addition of the polarization functions d and p for all atoms.

3. Results and discussion

The heterodiphosphane Ru-compound **1** has been screened in the imine hydrogenation reaction, using different reaction media (*i.e.* toluene, THF, MeOH or TFE) and imine substrates. The catalytic performance of **1** was compared to that of the related homodiphosphane counterparts **2** [10a] and **3** [10b], applying identical experimental conditions. The results of the catalytic reactions are shown in Table 1.

Table 1
Imine hydrogenation catalyzed by **1-3** in different reaction media.



P = P″Bu$_3$, P' = PPh$_3$ (**1**)
P = P' = P″Bu$_3$ (**2**)
P = P' = PPh$_3$ (**3**)

Entry	Precatalyst	Solvent	T(°C)/p(H_2) (bar)/t(h)	Substrate[a]	Conv.(%)
1	**1**	Toluene	90/50/3	A	8
2	**1**	THF	90/50/3	A	11
3	**1**	MeOH	90/50/3	A	92
4	**1**	TFE	90/50/3	A	100
5	**1**	MeOH	50/50/3	A	18
6	**1**	TFE	50/50/3	A	99
7	**1**	MeOH	50/50/3	B	27
8	**1**	MeOH	50/50/3	C	50
9	**1**	TFE	50/50/3	B	99
10	**1**	TFE	50/50/3	C	62
11	**1**	TFE	50/25/3	A	93
12	**2**	TFE	50/25/3	A	33
13	**3**	TFE	50/25/3	A	35
14	**1**	TFE	50/25/3	B	54
15	**1**	TFE	50/25/6	B	90
16	**1**	TFE	50/25/3	C	46
17	**1**	TFE	50/25/6	C	64

Catalytic conditions: precatalyst (0.005 mmol), substrate (0.5 mmol), solvent (8.0 mL), t (3 h).
[a] Substrate: A (N-benzylideneaniline), B (N-benzylidene-*p*-fluoroaniline), C (N-benzylidene-*p*-toluidine).

Regardless of the precatalyst and type of imine used, the corresponding secondary amine was the only organic product obtained.

A perusal of the catalytic results compiled in Table 1 shows that: (*i*) Under identical catalytic conditions alcohols (*i.e.*, MeOH or TFE) are much more suitable reaction media than toluene or THF (Table 1, entries 3 and 4 *vs* 1 and 2); (*ii*) Regardless of the substrate employed, TFE reveals to be the solvent of choice. In fact, much milder reaction conditions can be applied in TFE (*i.e*. 50 °C, 25 bar of dihydrogen); (*iii*) An increase of the Lewis-basicity of the imine nitrogen atom decreases the catalytic activity (entry 11 *vs* 14 and 16); (*iv*) **1** proves to be significantly more active than the homo-diphosphane counterparts **2** and **3**. This latter experimental fact might be rationalized by a faster conversion of **1** into catalytically active hydride species (*i.e.* mono- and dihydride) compared to **2** and **3**, as previously observed [12,14].

In order to shed light on the nature of the Ru-hydride species formed under catalytic imine hydrogenation conditions, *operando* (HP) NMR experiments were carried out with **1** in different reaction media such as 1:1 (v:v) solvent mixtures of C_6D_6/TFE, C_6D_6/MeOH or neat C_6D_6.

Selected $^{31}P\{^1H\}$ and ^1H NMR spectra, acquired under identical experimental conditions (*i.e*. 50 °C, 50 bar of dihydrogen pressure, without substrate) are shown in Fig. 1.

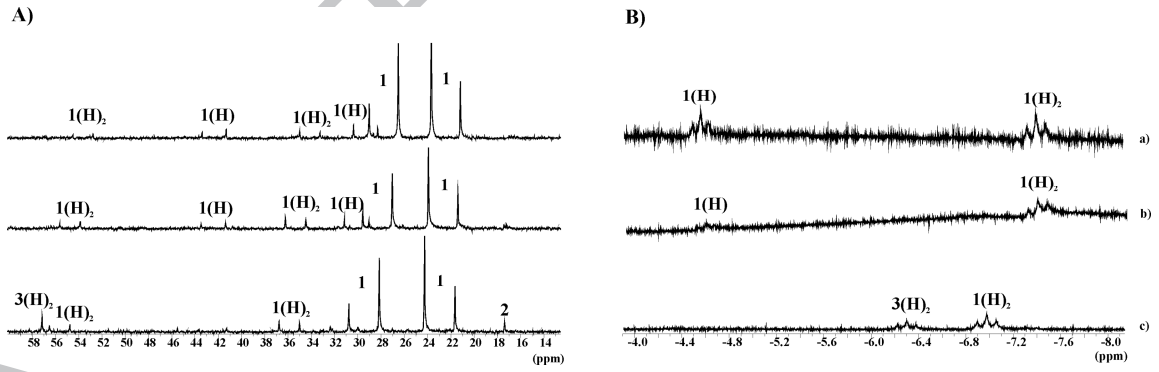


Fig. 1. *Operando* (HP) NMR spectra of **1** acquired at 50 °C in different reaction media in the presence of dihydrogen (50 bar): A) ($^{31}P\{^1H\}$ NMR spectra; B) Hydride region of the ^1H NMR spectra: (a) 1:1 (v:v) C_6D_6/TFE solvent mixture; (b) 1:1 (v:v) C_6D_6/MeOH solvent mixture and (c) neat C_6D_6.

The $^{31}P\{^1H\}$ and ^1H NMR spectra (*i.e.* only hydride region is shown) presented in Fig. 1 clearly demonstrate that: (*i*) **1** is only partially converted into hydride species, regardless of the reaction

solvent employed. (*ii*) In the presence of alcohols (*i.e.* TFE or MeOH) **1** is converted into the monohydride $[RuH(OAc)(CO)_2(P^nBu_3)(PPh_3)]$ (**1(H)**) and the dihydride species $[RuH_2(CO)_2(P^nBu_3)(PPh_3)]$ (**1(H)$_2$**) (Fig.1, traces a and b). Both latter hydrides are in equilibrium with **1**. **1(H)** is further in equilibrium with **1(H)$_2$** and 1 molequivalents of HOAc [12,14]. (*iii*) The molar ratio between **1(H)** and **1(H)$_2$** depends strongly on the type of alcohol present (*i.e.* in the presence of TFE a **1(H)/1(H)$_2$** molar ratio of almost 2 was determined by integration of the hydride NMR signals (Figure 1, trace a), whereas in the presence of MeOH the latter ratio was inverted. (*iv*) In neat C_6D_6, **1** transforms into **1(H)$_2$**, **2** and the dihydride of **3** (**3(H)$_2$**) (Fig. 1, trace c) [14]. **2** and **3(H)$_2$** are obtained as a result of a phosphane ligand scrambling reaction, as observed previously [14].

Analogous *operando* (HP) NMR spectra, acquired in neat C_6D_6 or using an 1:1 (v:v) C_6D_6/TFE solvent mixture under identical catalytic conditions as reported above but in the presence of substrate (*i.e.* N-benzilideneaniline), showed **1** as the only phosphorus containing species in case an 1:1 (v:v) C_6D_6/TFE solvent mixture was used, corroborating the fact that **1(H)** enters the catalytic cycle, and depresses the formation of **1(H)$_2$**. In contrast, in neat C_6D_6, the same NMR pattern as shown in Fig. 1 (trace c) was observed (Supporting information), which is indicating that neither hydride species formed in C_6D_6 (*i.e.* **3(H)$_2$** and **1(H)$_2$)** were catalytically active. In fact, a very scarce catalytic activity was found in toluene (Table 1, entry 1).

In order to elucidate the influence of a protic solvent on the equilibrium between the hydride species **1(H)** and **1(H)$_2$**, we studied in separate NMR experiments the protonation of synthesized **1(H)$_2$** with HOAc in the presence of MeOH or TFE. To this purpose, identical C_6D_6 solutions of **1(H)$_2$** were treated with TFE/HOAc or MeOH/HOAc (*i.e.* 1:1 (v:v) C_6D_6/alcohol, 0.4 mL of alcohol and 1.0 moleq of HOAc with respect to **1(H)$_2$**). The conversion of **1(H)$_2$** into **1(H)** was followed by ^1H and $^{31}P\{^1H\}$ NMR spectroscopy and selected ^1H NMR spectra (*i.e.* hydride region) of the latter spectroscopic study are shown in Fig. 2.

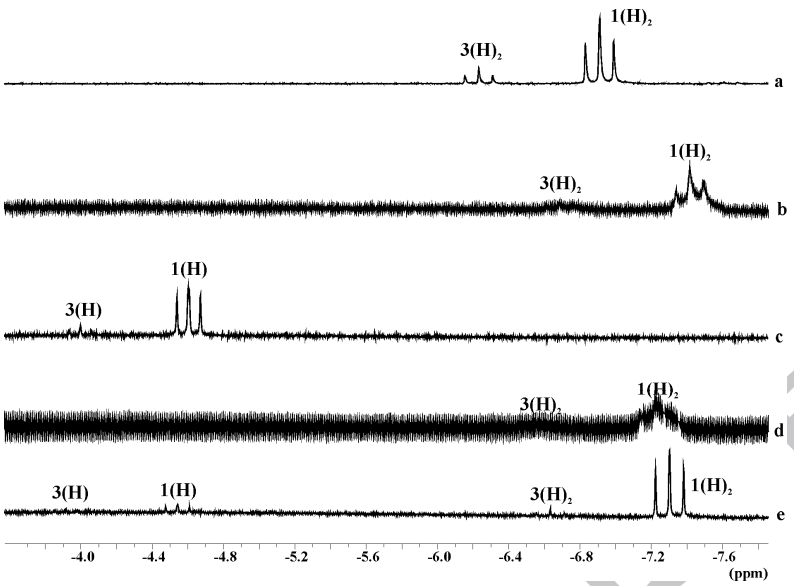


Fig. 2. Selected ^{1}H NMR spectra (hydride region) concerning the protonation reaction of **1(H)$_2$**: (a) **1(H)$_2$** in C_6D_6; (b) **1(H)$_2$** in 1:1 (v:v) C_6D_6/TFE; (c) after addition of HOAc to the latter solution and spectra acquisition after 2 h; (d) **1(H)$_2$** in 1:1 (v:v) C_6D_6/MeOH; (e) after addition of HOAc to the latter solution and spectra acquisition after 2 h.

A small amount of **3(H)$_2$** is formed during the synthesis of **1(H)$_2$** as shown in Fig. 2, trace a. The addition of equal amounts of TFE and MeOH to the C_6D_6 solution of **1(H)$_2$** (Fig. 2, trace b and d, respectively) leads to a shift and broadening of the hydride signal compared to the spectrum acquired in neat C_6D_6 (Fig. 2, trace a). This spectroscopic behaviour is due to the formation of hydrogen bonds between the hydride atoms of **1(H)$_2$** and the hydroxyl group of the alcohol [15]. **1(H)$_2$** is stable in the presence of alcohols, characterized by a different p*Ka* value (*i.e.* 12.4 (TFE) and 15.5 (MeOH)) [16] and upon addition of HOAc to the latter solvent mixtures of **1(H)$_2$**, conversion to **1(H)** takes place, which is complete after 2 h in case TFE is present in the solvent mixture (Fig. 2, trace c), whereas for the same time interval trace amounts of **1(H)** were formed in an 1:1 (v:v) C_6D_6/MeOH solvent mixture (Fig. 2, trace e). This experimental result led us to conclude, that TFE, in contrast to MeOH, significantly accelerates the protonation of **1(H)$_2$** shifting the equilibrium towards **1(H)**. As a consequence, even in the presence of dihydrogen, **1(H)** is the dominant hydride species formed in the presence of TFE, as shown by the corresponding (HP) NMR experiment (Fig. 1, trace a). Hence the catalytic activity observed is strongly related to the

amount of **1(H)** present in equilibrium with **1** in different reaction media. As a result, under identical experimental conditions, imine hydrogenation reactions conducted in TFE showed much higher substrate conversion compared to MeOH (Table 1).

Since (HP) NMR experiments conducted in C6D6/TFE in the presence of **1** and substrate confirmed the absence of **1(H)** and **1(H)$_2$**, we deem **1(H)** as the hydride species that enters the catalytic cycle. Moreover, **1(H)$_2$**, in contrast to **1(H)**, is not endowed with an easily removable ligand, which is a prerequisite for the catalytic activity.

DFT-calculations performed with the model compound [Ru(OAc)$_2$(CO)$_2$(PMe$_3$)(PPh$_3$)] (**1'**) (*i.e.* PMe$_3$ was chosen for simplicity reasons. PMe$_3$ has a slightly smaller cone angle than P^{n}Bu$_3$ (118° *vs* 132 °) [17], while the electronic properties are comparable. The relative free energy profile for the conversion of **1'** into the model Ru-monohydride-acetate species **6'** in TFE is depicted in Fig. 3.

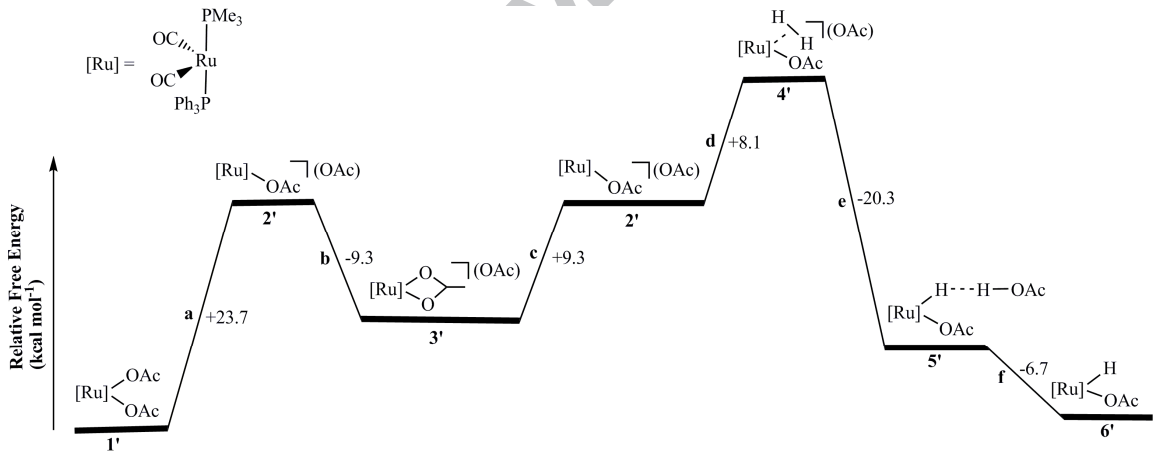


Fig. 3. Relative free energy profile for the conversion of **1'** into **6'** in TFE.

The crucial reaction steps for the latter conversion are: (*i*) The dissociation of acetate from **1'** giving the penta-coordinated intermediate **2'**, which is stabilized by an κ^2-*O,O*-acetate coordination (**3'**); (*ii*) The coordination of dihydrogen to **2'** forming the non-classical dihydrogen complex **4'** [18] and (*iii*) the heterolytic dihydrogen splitting assisted by the free acetate anion (*i.e.* no transition state (TS) was observed for the latter reaction, which we followed by a relaxed energy scan

(Supporting information)). An alternative intramolecular acetate-triggered dihydrogen activation turned out to be ca. 6.0 kcal mol^{-1} less favourable compared to the intermolecular version. The dissociation of acetic acid from Ru-monohydride HOAc adduct **5'** gives the Ru-monohydride actetate species **6'**.

Analogous DFT calculations regarding MeOH instead of TFE as reaction medium, gave an almost identical free energy profile (Supporting information). In contrast, DFT calculations performed with **1'** in C_6H_6 showed that PPh_3 dissociation from metal centre is much more favoured over the acetate dissociation to provide a free coordination site at ruthenium (*i.e.* +22.8 kcal mol^{-1} and +61.9 kcal mol^{-1} for PPh_3 and acetate dissociation, respectively) (Supporting information). This latter result is in agreement with the behaviour reported for **1** in C_6H_6 solution [14]. According to DFT calculations **6'** enters the catalytic cycle by an acetate dissociation along with the formation of a pentacoordinated Ru-species **7'** (Fig. 4). We also investigated the possible protonation of coordinated acetate in **6'** by TFE [19]. As a result, two protonated isomeric Ru-species of the formula $[RuH(HOAc)(CO)_2(PMe_3)(PPh_3)]^+$ were obtained. DFT-calculations revealed the carboxyl oxygen atom to be more prone to protonation compared to the Ru-coordinated oxygen atom (*i.e.* +34.0 kcal vs 39.1 kcal mol^{-1}). In any case, acetate protonation is associated to significantly higher free activation enthalpy compared to acetate dissociation from **6'**. **7'** might have two possibilities to enter the catalytic cycle in TFE as reaction medium, either by TFE (Fig. 4) or imine coordination (*i.e.* $CH_3CH{=}NCH_3$ has been chosen as model imine) (Fig. 4).

The coordination of TFE to **7'** gives **8'**, which is the key species for the TFE-assisted outer sphere imine hydrogenation mechanism as shown in Fig. 4.

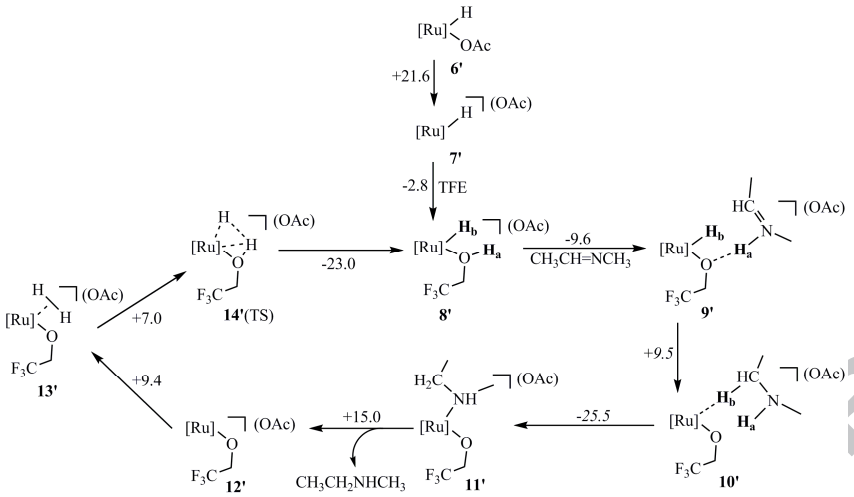


Fig. 4. Proposed catalytic cycle for the **8'**-catalyzed imine hydrogenation reaction in TFE. ΔG and ΔE (italics) values are reported in kcal mol^{-1}.

8' transfers barrierless H^+ (H_a) from coordinated TFE solvent molecule to the anchored imine nitrogen atom giving intermediate **9'** (Fig. 4). In contrast, the protonation of the imine substrate by acetic acid (Supporting information), instead of coordinated TFE, giving an iminium compound, which accepts H^- [20], is endergonic by +9.1 kcal mol^{-1}. The positive charge of the iminium carbon atom fosters the H^- transfer from Ru to the iminium carbon atom leading to the amine adduct **10'**. This latter reaction is associated to a ΔE of +9.5 kcal mol^{-1} (*i.e.* since no TS was observed for the latter reaction step, a relaxed energy scan of the C(imine)-Ru-hydride intermolecular distance in **9'** was carried out (Supporting information). Notable, the H^+/H^- transfer in TFE is significantly more favoured compared to MeOH (*i.e.* -0.1 kcal mol^{-1} (TFE) *vs* +10.3 kcal mol^{-1} (MeOH)) (Supporting information).

The amine formed coordinates to Ru giving species **11'**. The regeneration of the key catalytic species **8'** comprises: (*i*) The dissociation of the coordinated amine from **11'** (*i.e.* this reaction step is expected to strongly depend on the Lewis-basicity of the amine; accordingly we found a drop of the substrate conversion on increasing Lewis-basicity of the imine nitrogen atom (Table 1)). (*ii*) The coordination of dihydrogen to **12'** is followed by an alkoxy group-assisted, heterolytic dihydrogen

splitting reaction [14,18]. A **8'**-related Ru-species was proposed as catalyst for the ligand-assisted outer-sphere hydrogenation of CO_2 to formic acid [21].

The coordination of the model imine to the penta-coordinated intermediate **7'** giving **15'** is the initial step of a classical inner-sphere imine hydrogenation mechanism (Fig. 5). Although the imine coordination to **7'** is favoured over the TFE coordination (*i.e.* ΔG = -22.2 kcal mol^{-1} (imine coordination) *vs* -2.8 kcal mol^{-1} (TFE coordination), the inner-sphere reaction mechanism shows a high activation barrier for the hydride migration (*i.e.* +21.5 kcal mol^{-1} (inner-sphere) *vs* +9.5 kcal mol^{-1} (outer sphere)) to give the penta-coordinated Ru-amido complex **16'** [7]. A relaxed energy scan of the latter reaction revealed no TS, instead a continuously increasing energy upon diminishing the Ru-H···C(imine) distance was observed (Supporting information).

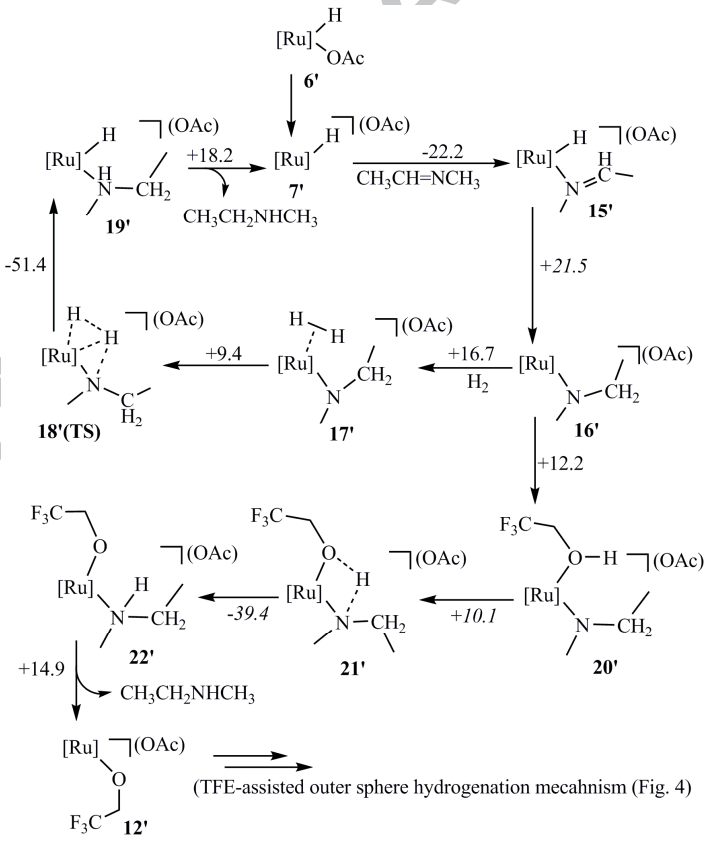


Fig. 5. Proposed catalytic cycle for the **7'**-catalyzed imine hydrogenation reaction in TFE. ΔG and ΔE (italics) are reported in kcal mol^{-1}.

Moreover, the regeneration of catalyst **7'** foresees an intramolecular protonation reaction mediated either by coordinated dihydrogen (*i.e.* Fig. 5, intermediates **17'** through **19'**) or by coordinated TFE (*i.e.* intermediates **20'** through **12'**). In the latter case **12'** is formed which enters the outer-sphere reaction mechanism (Fig. 4).

Importantly, not only the hydride migration in the inner-sphere mechanism is associated to a high activation energy but also the regeneration of the catalyst **7'** needs much higher activation energies compared to the outer-sphere reaction mechanism, making it hence less probable to be operative.

4. Conclusions

$[Ru(OAc)_2(CO)_2(P^nBu_3)(PPh_3)]$ (**1**) was employed as precatalyst for the selective hydrogenation of imines to the corresponding secondary amine carried out in different reaction media in the absence of an additional base. (HP) NMR experiments carried out with **1** in the presence of an alcohol reaction medium (*i.e.* MeOH, 2,2,2-trifluoroethanol (TFE)) and in the absence of substrate clearly showed the formation of the corresponding mono- **1(H)** and dihydride **1(H)$_2$**, which are in equilibrium with **1** (*i.e.* main species even under catalytic conditions). The type of alcohol determined the molar ratio between **1(H)/1(H)$_2$**, showing for TFE the highest ratio, which is associated to a much higher catalytic activity found in TFE compared to MeOH. DFT calculations carried out with a model compound of **1** in TFE and MeOH, indicated an alcohol-assited outer-sphere reaction mechanism as the most probable catalytic imine hydrogantion mechanism. In this respect, TFE showed, in contrast to MeOH, an almost barrierless H^+/H^- transfer to the imine substrate.

Acknowledgements

G.M. And A.I. acknowledge ISCRA-CINECA HP grant "HP10BNL89W" and CREA (Centro Ricerche Energia e Ambiente) of Colle Val d'Elsa (Siena, Italy) for computational resources.

Appendix A: Supplementary material

Operando (HP) NMR spectra of **1** acquired in the presence of substrate and supporting DFT calculations. Supplementary data associated with this article can be found, in the online version , at http://dx.doi.org/...

References

[1] (a) C.T. Nugent, M. El-Shazly, Adv. Synth. Catal. 352 (2010) 753; (b) J.-H. Xie, S.-F. Zhu, Q.-L. Zhou, Chem. Rev. 111 (2011) 1713; (c) N. Fleury-Brégeot, V. de la Fuente, S. Castillón, C. Claver, ChemCatChem 2 (2010) 1346.

[2] (a) C.P. Casey, J.B. Johnson, J. Am. Chem. Soc. 127 (2005) 1883; (b) J.S.M. Samec, A.H. Éll, J.B. Aberg, T. Privalov, L. Eriksson, J.-E. Bäckvall, J. Am. Chem. Soc. 128 (2006) 14293; (c) A. Comas-Vives, G. Ujaque, A. Lledós, Organometallics 27 (2008) 4854; (d) T. Privalov, J.S. Samec, J.-E. Bäckvall, Organometallics 26 (2007) 2840.

[3] (a) S. Hashiguchi, A. Fuji, J. Takehara, T. Ikariya, R. Noyori, J. Am. Chem. Soc. 117 (1995) 7562; (b) J. Václavík, M. Kuzma, J. Přech, P. Kačer, Organometallics 30 (2011) 4822; (c) P. Šot, M. Kuzma, J. Václavík, J. Pecháček, J. Přech, J. Januščák, P. Kačer, Organometallics 31 (2012) 6496.

[4] (a) S.E. Clapham, A. Hadzovic, R.H. Morris, Coord. Chem. Rev. 248 (2004) 2201; (b) A. Comas-Vives, G. Ujaque, A. Lledós, Adv. Inorg. Chem. 62 (2010) 231; (c) O. Eisenstein, R.H. Crabtree, New. J. Chem. 37 (2013) 21.

[5] (a) C.P. Casey, S.W. Singer, D.R. Powell, R.K. Hayashi, M. Kavana, J. Am. Chem. Soc. 123 (2001) 1090; (b) M. Martín , E. Sola, S. Tejero, J.L. Andrés, L.A. Oro, Chem. Eur. J. 12 (2006) 4043.

[6] (a) R.M. Bullock, Chem. Eur. J. 10 (2004) 2366; (b) M.P. Magee, J.R. Norton, J. Am. Chem. 123 (2001) 1778; (c) H. Guan, M. Limura, M. P. Magee, J.R. Norton, G. Zhu, J. Am. Chem. Soc. 127 (2005) 7805; (d) M. Martín, E. Sola, S. Tejero, J.A. López, L.A. Oro, Chem. Eur. J. 12 (2006) 4057.

[7] (a) H. Grützmacher, Angew. Chem. Int. Ed. 47 (2008) 1814; (b) M. Käß, A. Friedrich, M. Drees, S. Schneider, Angew. Chem. Int. Ed. 48 (2009) 905.

[8] (a) N. Arai, N. Utsumi, Y. Matsumoto, K. Murata, K. Tsutsumi, T. Ohkuma, Adv. Synth. Catal. 354 (2012) 2089; (b) C.J. Cobley, J.P. Henschke, Adv. Synth. Catal. 345 (2003) 195; (c) M. Vaquero, A. Suárez, S. Vargas, G. Bottari, E. Álvarez, A. Pizzano, Chem. Eur. J. 18 (2012) 15586; (d) K. Abdur-Rashid, R. Guo, A.J. Lough, R.M. Morris, D. Song, Adv. Synth. Catal. 247 (2005), 571.

[9] (a) A. Salvini, P. Frediani, C. Giannelli, L. Rosi, J. Organomet. Chem. 690 (2005) 371; (b) F. Micoli, L. Salvi, A. Salvini, P. Frediani, C. Giannelli, J. Organomet. Chem. 690 (2005) 4867.

[10] (a) M. Bianchi, P. Frediani, U. Matteoli, G. Menchi, F. Piacenti, G. Petrucci, J. Organomet. Chem. 259 (1983) 207; (b) S.D. Robinson, M.F. Uttley, J. Chem. Soc., Dalton Trans. (1973) 1912.

[11] C. Bianchini, A. Meli, A. Traversi, Ital. Pat. FI A,000,025 (1997).

[12] L. Salvi, A. Salvini, F. Micoli, C. Bianchini, W. Oberhauser, J. Organomet. Chem. 692 (2007) 1442.

[13] (a) S. Grimme, J. Chem. Phys. 124 (2006) 34108; (b) V. Barone, M. Cossi, J. Phys. Chem. A 102 (1998) 1995; (c) M. Cossi, N. Rega, G. Scalmani, V. Barone, J. Comput. Chem. 24 (2003) 669; (d) M. Dolg, H. Stoll, H. Preuss, R.M. Pitzer, J. Phys. Chem. 97 (1993) 5852.

[14] F. Micoli, W. Oberhauser, A. Salvini, C. Bianchini, J. Organomet. Chem. 692 (2007) 2334.

[15] E.I. Gutsul, N.V. Belkova, M.S. Sverdlov, L.M. Epstein, E.S. Shubina, V.I. Bakhmutov, T.N. Gribanova, R.M. Minyaev, C. Bianchini, M. Peruzzini, F. Zanobini, Chem. Eur. H. 9 (2003) 2219.

[16] J. Wu, J.H. Barnard, Y. Zhang, D. Talwar, C.M. Robertson, J. Xiao, Chem. Commun. 49 (2013) 7052.

[17] C.A. Tolman, Chem Rev. 77 (1977) 313.

[18] G.J. Kubas, Chem. Rev. 107 (2007) 4152.

[19] D. Donghi, T. Beringhelli, G. D'Alfonso, M. Mondini, Chem. Eur. J. 12 (2006) 1016.

[20] (a) M.C. Carrión, M. Ruiz-Castaneda, G. Espino, C. Aliende, L. Santos, A.M. Rodríguez, B.R. Manzano, F.A. Jalón, A. Lledós, ACS Catal. 4 (2014) 1040; (b) J.E.D. Martins, G.J. Clarkson, M. Willis, Org. Lett. 11 (2009) 847.

[21] S.M. Ng, C. Yin, C.H. Yeung, T.C. Chan, C.P. Lau, Eur. J. Inorg. Chem. (2004) 1788.

Caption to the figures

Fig. 1. *Operando* (HP) NMR spectra of **1** acquired at 50 °C in different reaction media in the presence of dihydrogen (50 bar): A) ($^{31}P\{^{1}H\}$ NMR spectra; B) Hydride region of the ^{1}H NMR spectra: (a) 1:1 (v:v) C_6D_6/TFE solvent mixture; (b) 1:1 (v:v) C_6D_6/MeOH solvent mixture and (c) neat C_6D_6.

Fig. 2. Selected ^{1}H NMR spectra (hydride region) concerning the protonation reaction of **1(H)$_2$**: (a) **1(H)$_2$** in C_6D_6; (b) **1(H)$_2$** in 1:1 (v:v) C_6D_6/TFE; (c) after addition of HOAc to the latter solution and spectra acquisition after 2 h; (d) **1(H)$_2$** in 1:1 (v:v) C_6D_6/MeOH; (e) after addition of HOAc to the latter solution and spectra acquisition after 2 h.

Fig. 3. Relative free energy profile for the conversion of **1'** into **6'** in TFE.

Fig. 4. Proposed catalytic cycle for the **8'**-catalyzed imine hydrogenation reaction in TFE. ΔG and ΔE (italics) values are reported in kcal mol^{-1}.

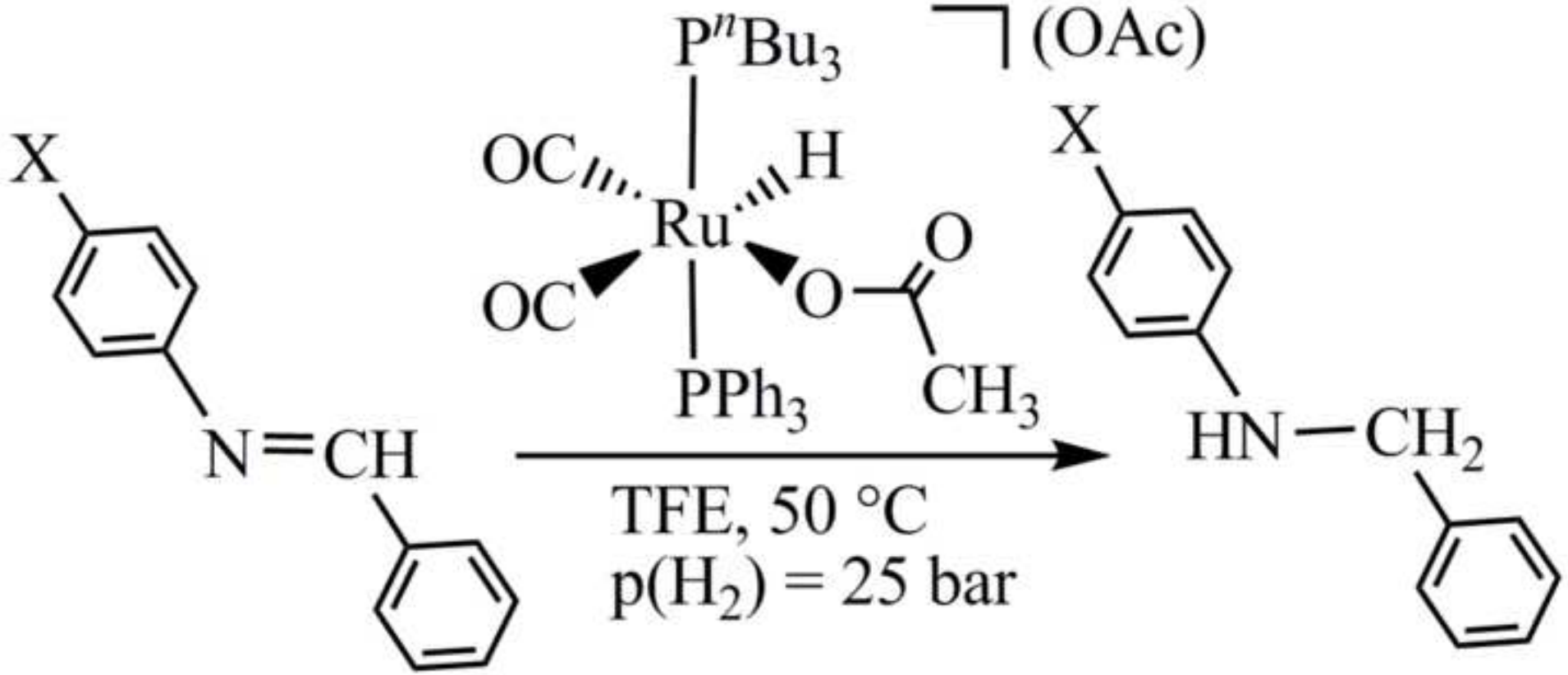
Fig. 5. Proposed catalytic cycle for the **7'**-catalyzed imine hydrogenation reaction in TFE. ΔG and ΔE (italics) are reported in kcal mol^{-1}.

- Base-free imine hydrogenation with $[Ru(OAc)_2(CO)_2(P^nBu_3)(PPh_3)]$ (1) in different reaction media.

- 2,2,2-trifluoroethanol (TFE) emerged as the solvent of choice for the 1-catalyzed imine hydrogenation under mild conditions.

- TFE stabilizes very efficiently the monohydride of 1, which enters the catalytic cycle.

-A TFE-assisted outer-sphere reaction mechanism is favored over a classical inner-sphere reaction mechanism.



X = H, F, Me

TFE = 2,2,2-Trifluoroethanol

Graphical abstract - synopsis

$[Ru(OAc)_2(CO)_2(P^nBu_3)(PPh_3)]$ was used as precatalyst to hydrogenate selected imines to the corresponding amine in different reaction media and under base-free conditions. The solvent of choice revealed to be 2,2,2-trifluoroethanol (TFE) which directly participated in an TFE-assisted outer-sphere reaction mechanism by forming a Ru-monohydrate-TFE intermediate.