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Homogeneous hydrogenation of fluoroaromatic imines with Ni compounds, evidence for η^2-C=N intermediate in the catalytic cycle

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ABSTRACT

The catalytic hydrogenation of a series of fluorinated imines with $[Ni(dippe)(\mu\text{-}H)]_2$ dippe = 1,2 bis(diisopropylphosphino)ethane was undertaken and the effect of solvent, temperature, and hydrogen pressure on reactivity assessed. High conversions of fluorinated imines into amines were obtained in methanol, under relatively mild temperature and pressure conditions; a transfer hydrogenation process was found to take place *in situ*, when using nickel catalysts. The use of H_2 pressure was therefore required to drive reactions to completion. In particular, electron poor imines were hydrogenated at a faster rate than the electron-rich ones. A mechanistic proposal involving a π-coordinated imine as a key intermediate is presented.

1. Introduction

The hydrogenation of imines to amines is an important transformation in current synthetic chemistry; amines being important building blocks for the pharmaceutical and fine chemical industry [1]. Its main disadvantage however, relies on the poor reactivity that is exhibited by C=N moieties for conventional organic methodologies [2] and thus, their activation using transition metal complexes has gathered much interest in recent years although remaining a challenging goal. Mechanistically, the hydrogenation of imines is even less understood: their study been hampered by the rather forceful conditions that are usually employed in this reaction; in general, even more harsh than those needed for the hydrogenation of other types of unsaturated substrates such as olefins or ketones [3]. The latter, usually interact with metal centers through the formation of π-bonded (*side on* coordinated) compounds; a feature that is normally conceived within proposals for catalytic processes involving such substrates. In the case of imines however, the fact that σ- or *end on* coordination is also feasible through the lone pair of the nitrogen atom, seems to have opposed an additional drawback in terms of achieving proper understanding of their catalytic cycles [4]; the number of active isolated compounds depicting a η^2- or side on coordination of an imine being, much less common than the former ones, although a number of examples including both monometallic and bimetallic systems, have been reported [5,6].

The hydrogenation of C=N bonds [7] is normally performed by late transition metals such as Rhodium [8], Ruthenium [9], and Iridium [10]; some additional reports using early transition metals such as Titanium [11] and different lanthanides [12], also been informed. The η^2-coordination of the imine to the metal center has been proposed to occur within the catalytic cycles of several of these metals and in particular [2b,3b,c,6,8a], the use of an alcoholic solvent has been proposed to assist in the formation of the π-bound intermediates, presumably by hydrogen bonding with the coordinated substrate [3c,8a]. Fryzuk [6] has informed the apparition of this type of intermediate by ^{1}H NMR; a result of the migratory insertion of a coordinated imine to a Rh(I)-H bond in a bimetallic compound; albeit never been isolated.

For a number of years, our group has been interested in the activation of C—CN bonds using low oxidation-state metals and has reported the η^2-*C,N* coordination of a variety of aliphatic, aromatic and heteroaromatic nitriles, including cyanoquinolines and cyanopyridines, to the nickel(0) moiety [(dippe)Ni] [13]; the cleavage of the C—CN bond been also observed to take place with an important number of these after a mild heating and even at room temperature, under photochemical conditions, and only in the case of aromatic nitriles, has this process been found to be reversible. Recently, this chemistry has been expanded to the catalytic isomerization of cyano olefins using [Ni(0)] compounds

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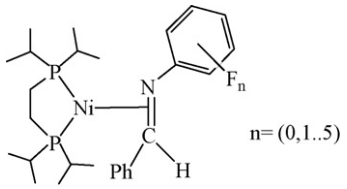
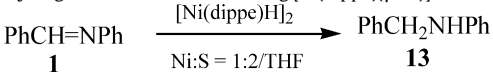


Fig. 1. General structure of imine complexes.

bearing diphosphine auxiliary ligands and a number of important intermediates of the process, particularly involving the cleavage of the C—CN bond *in situ* were successfully isolated [14]. The functionalization of η^2-coordinated —CN bonds to nickel(0) has also been addressed although from an entirely different perspective to the C—CN bond cleavage and from this, the homogeneously catalyzed selective hydration of benzo- and acetonitrile to their corresponding carboxamides [15], or as in the case of the industrially relevant dinitriles, 1,2-, 1,3-, and 1,4-dicyanobenzenes, to the bis-amido, amido/carboxyl, or bis-carboxyl hydration products [16]; have been successfully undertaken. The formation of *side-on* coordinated N(H)═C(OH)—R intermediates has been proposed to be formed *in situ* as a result of water addition to η^2-bound nitriles within the catalytic cycles in those processes. Related to this, a series of Ni(0) complexes of the type [(dippe)Ni(η^2-(*C,N*)-PhHC═NR′)] bearing fluorinated imines have also been recently reported by our group (see Fig. 1) [17].

The *side on* coordination of the C═N bond in those substrates to the 14e fragment [(dippe)Ni] was observed to take place and from it, reactivity studies involving direct hydrogenation reactions was preliminary explored at the time; the use of group 10 metals, although usually the catalysts of choice for the heterogeneous hydrogenation of imines (*i.e. in situ* reduction of Ni(II) salts to metallic nickel) [18], rarely been envisioned as the likely catalysts for an homogeneous process. To the best of our knowledge, only a few reports using Pd(II) (diphosphine) complexes [19], Ni(II) and Pd(II) salen type complexes [20],or Ni(0) carbene compounds [21] have been informed and of these, only the latter along with W-2 Raney-Nickel (heterogeneous) [18c] have been reported for transfer hydrogenation reactions over imines. In the case of nickel, the fact that it appears as a relatively inexpensive metal makes of its use an attractive alternative. Herein, we have continued with our studies involving the hydrogenation of imines coordinated to nickel(0) compounds and we now report evidences for the transfer hydrogenation reaction over C═N moieties using a methanol/H_2 coupled system. A mechanistic proposal for this transformation is also addressed.

Table 1
Hydrogenation of substrate **1** using [Ni(dippe)(μ-H)]$_2$[a].



Entry	T (°C)	t (h)	Conv. (%)[b]
1	25	24	3
2	75	24	5
3	100	24	10
4	140	24	20
5	140	96	29
6	140	96	36[c]
7	160	96	13[c]
8	180	96	8[c]

[a] General reaction conditions: stainless steel autoclave pressurized at 60 psi of H_2, using 30 mL THF as solvent. Stoichiometric conditions: Ni/substrate 1:2; [Ni(dippe)(μ-H)]$_2$ 0. 0808 mmol, imine **1** 0.1617 mmol.

[b] Conversion determined by GC–MS, with respect to the amount of starting substrate.

[c] 1 mol% of catalytic precursor.

2. Results and discussion

2.1. Hydrogenation studies

Fluorine containing organic molecules such as amines are important provided that the introduction of fluorine in them (*i.e.* as in fluorine containing building blocks) can profoundly alter their physical, chemical and biological properties [22] and as a result of this, the interest in achieving their synthesis by means of reductive processes has been increasing in the recent years [23]. To the best of our knowledge, no catalytic reduction of fluorinated imines has been informed thus far, and neither has the effect of the number and position of the fluorine substituents over the reactivity of this ligands been studied. Fig. 2 illustrates the examples used in the current work.

The reduction of substrate **1** to *N*-phenyl-benzyl-amine, **13**, was selected as a model reaction given its similarity with industrially important *N*-aryl-imines [3c], and was thus assessed under a variety of different conditions using THF as the solvent; the results of which are summarized in Table 1 (*vide infra*). Under stoichiometric conditions in general (entries 1–4), conversion was found to be mostly temperature dependent, an increment from 3 to 20% of the corresponding amine been found upon the increase in reaction time from 24 to 96 h at the higher temperature limit of 140 °C, barely resulting in an improved conversion of 29% (entries 4 and 5, in the Table). The use of catalytic conditions at 140 °C (Entry 5) yielded a 36% conversion; an increase in temperature to 160 °C and above resulting in smaller numbers, probably due

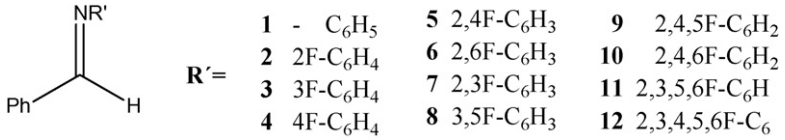
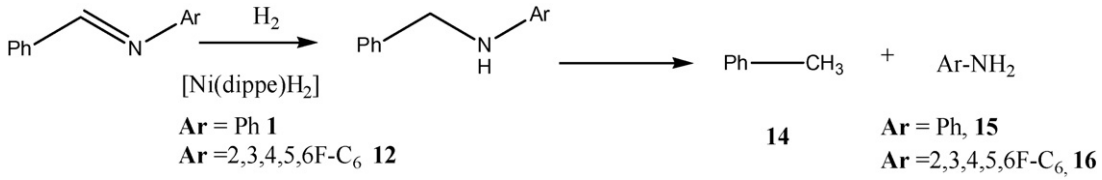


Fig. 2. Used imines.



Scheme 1.

Table 2
Hydrogenation of **1** using $[Ni(dippe)(\mu\text{-}H)]_2$[a].

Entry	T (°C)	Solvent	t (h)	P (psi)	Conv. (%)[a]
1	25	THF	24	60	3
2	25	THF	24	225	<1
3	100	THF	24	225	27[b]
4	100	CH_3OH	24	225	92[b]
5	100	CH_3OH	12	225	90[b]

[a] General conditions: Monel autoclave; stoichiometric conditions Ni/S 1:2; $[Ni(dippe)(\mu\text{-}H)]_2$ 0.0808 mmol, imine **1** 0.1617 mmol.
[b] Conversion determined by GC–MS subtracting the amount of unreacted substrate.

to catalyst decomposition (entries 7 and 8, in the Table) [24]. Under similar reaction conditions, the reduction of substrate **12** to benzyl-pentafluorophenyl-amine was also poor (see Supporting Information, SI); the change for a solvent with higher boiling point and polarity such as xylene, resulting in little effect on conversion; the hydrogenation reaction for this particular substrate attempted at 140 °C, resulting in <10% conversion of its hydrogenolysis products (Indicated in SI); toluene **14** and pentafluoro aniline **16** detected by GC–MS (Scheme 1) [25]. For the imine PhCH=NPh, both toluene and aniline **15** were detected when the reaction was performed at 180 °C; a closely related reaction recently reported for Ru(II) dihydride complexes [1c].

An increase in H_2 pressure and temperature in THF improved the conversion from imine **1** to amine **13** (Table 2, 10%, entry 1, *vs.* 27%, entry 3). Additionally, on increasing the polarity from THF to methanol (both with same donor number) [8c,26], allowed us to reach milder reaction conditions with a considerable increase in yield (Table 2, 27% entry 3, *vs.* 90%, entries 4 and 5). As mentioned earlier for **1**, its entire reduction was achieved under stoichiometric conditions (*vide supra*). No conversion was achieved under catalytic conditions (Table 3, entry 1) and thus, the reaction with the fluorinated imine **12** was scaled to 2 mol% Ni(0). A progressive decrease in time (from 24 to 3 h) did not affect conversion, 99% conversion achieved within 3 h (Table 4, entries 1–3); an 89% conversion obtained in 1 h (Table 4, entry 4). To note, a decrease in H_2 pressure lead to an incomplete substrate conversion of 41% (Table 4, entry 5). Several experiments were run as blanks, changing one parameter at a time (Table 5, Section 5); no significant reduction to benzyl-(2,3,4,5,6-pentafluoro-phenyl)-amine **17** (1%) was observed [27].

Table 3
Hydrogenation reactions over several imines using 1 mol% of $[Ni(dippe)(\mu\text{-}H)]_2$[a] as catalytic precursor dissolved in methanol.

Entry	Substrate	Conv (%)[b]
1	$-C_6H_5$	<1
2	$-2F\text{-}C_6H_4$	<1
3	$-3F\text{-}C_6H_4$	<1
4	$-4F\text{-}C_6H_4$	<1
5	$-2,4\text{-}F\text{-}C_6H_3$	<1
6	$-2,3\text{-}F\text{-}C_6H_3$	40[c]
7	$-2,6\text{-}F\text{-}C_6H_3$	70[c]
8	$-3,5\text{-}F\text{-}C_6H_3$	94[d]
9	$-2,4,5\text{-}F\text{-}C_6H_2$	83[c]
10	$-2,4,6\text{-}F\text{-}C_6H_2$	99[d]
11	$-2,3,5,6\text{-}F\text{-}C_6H$	99[c]
12	$-2,3,4,5,6\text{-}F\text{-}C_6H$	>99[d]

[a] General conditions: Monel autoclave pressurized at 225 psi of H_2, charged with methanol (30 mL); reaction time of 3 h, $T = 100$ °C.
[b] Conversion determined by GC–MS subtracting the isolated amount of unreacted substrate.
[c] Conversion determined by GC–MS and corroborated with ^{1}H NMR of crude mixture.
[d] Conversion determined by GC–MS only.

Table 4
Optimization of reaction conditions for benzylidene-pentafluorophenyl-aniline, **12**, at 100 °C in CH_3OH.

$$\underset{\mathbf{12}}{PhCH{=}N\text{-}2,3,4,5,6F\text{-}C_6} \xrightarrow[Ni(0):S = 1:50]{[Ni(dippe)H]_2} \underset{\mathbf{17}}{PhCH_2NH\text{-}2,3,4,5,6F\text{-}C_6}$$

Entry	T (h)	P (psi)	Conv. (%)[a]
1	24	225	>99
2	12	225	>99
3	3	225	99.4
4	1	225	89.0
5	3	60	41.0[b]

[a] Conversion was determined by GC–MS and corroborated by ^{1}H NMR of crude mixture.
[b] Conversion was determined by GC–MS using $PhCH_2NHPh$ as internal standard.

The remaining substrates were assessed following the reaction conditions optimized for **1** in the attempt of establishing the effect that varying both electron withdrawing and associated sterics due to fluorine substitution might have over imine reduction. As already mentioned, no reduction was observed for **1**, under catalytic conditions (Table 3, entry 1). In the case of the mono fluoro-substituted imines **2**–**4**, the position of the fluorine atom exhibited no effect on the resulting conversions (Table 3, entries 2–4).

Moderate to excellent conversions were observed with imines with two or more fluorine substituents over the aromatic ring. The conversion increased (although not linearly) with the number of fluorines on the aromatic moiety (Table 3, entries 10–12). In the apparent order of reactivity, polyfluorinated imines seemingly undergo the fastest hydrogenation from the series: the di- or tri-substituted aromatic imines increasingly achieving full conversions to their corresponding amines. In the case of **12**, complete reduction was observed to occur in 1 h, leading us to conclude that it is the large electron withdrawing nature drawn upon the C=N bond of this substrate, that mainly drives the hydrogenation reaction to completion; a trend that is seemingly reflected within the series. In terms of the position of the fluoro-substituent, moderate to good conversions were obtained for substrates with *meta*-substitutions (Table 3, entries 6 and 8). Similar behaviors have been informed for heterogeneous [18d] and homogeneously catalyzed hydrogenations of imines using platinum and palladium, respectively [19]. Apparently, the presence of an electron withdrawing (EW) group over the *meta*- and *para*-positions of the phenyl ring renders much more effective than an *ortho*-substituted system might probe; a circumstance that has been found to yield exactly the opposite in the case of some Ni(0) carbene complexes, the *ortho*-substituted imine giving the highest conversion and the *para*-substituted, the lowest [21]. Related to this last paragraph, it could also be predicted that the greater the EW character of the substituent over the phenyl

Table 5
Blank runs for **12**.

Entry	T(°C)	T (h)	P (psi)	Conv.[a] (%)
1[b]	25	3	225	<1%
2[b]	100	3	atm	1%
3[c]	100	3	225	NR
4	100	24	atm	8%[d,e]
5	100	72	atm	[e]

[a] Conversion was determined by GC–MS, and isolated amount of unreacted substrate.
[b] General conditions: Parr Reactor, solvent 30 mL methanol, 1 mol% of $[Ni(dippe)(\mu\text{-}H)]_2$.
[c] 0% $[Ni(dippe)(\mu\text{-}H)]_2$. No catalytic precursor.
[d] Conversion was determined by GC–MS.
[e] Formation of benzaldehyde dimethyl acetal, detected by ^{1}H NMR in $CDCl_3$ and GC–MS.

Table 6
Reactions for substrate **9**[a].

Entry	T (°C)	T (h)	P (psi)	Conv.[b] (%)
1	80	3	225	7
2	100	3	225	84[c]
3	100	1	225	6

[a] General conditions: Parr Reactor, solvent 30 mL methanol, 1 mol% of $[Ni(dippe)(\mu\text{-}H)]_2$.
[b] Conversion determined by GC–MS.
[c] Mercury drop experiment.

ring, the faster the kinetics may probe within the overall hydrogenation process: in the case of Pd systems for example, complete reduction of an *N*-substituted imine only informed to be feasible in the presence of extremely electronegative groups such as a tosyl or diphenylphosphynil [19,28].

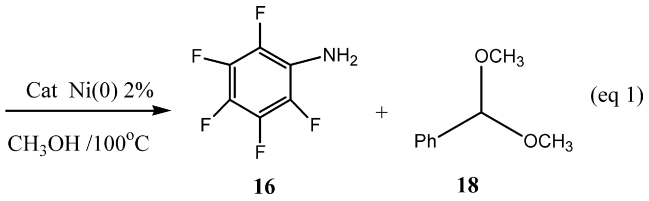
For substrates bearing di-*ortho* substitutions, lower conversions could be proposed on the basis of steric hindrance of the substituents. However, as observed with imines bearing three or even more fluorine substitutions, their greater electrophilic nature is enough to overcome the sterics; a moderate yield obtained from imine **6** (Table 3, entries 7–11), the best conversions been observed with the pentafluoro-substituted imine **12** (Table 3, entry 12).

Several experiments were undertaken as part of the current work, in the attempt of further optimizing both reaction time and temperature. Experiments were addressed at a lower temperature (80 °C) and shorter times (1 h), but a dramatic drop in conversion was ultimately observed (Table 6, entry 1 and 3, see Section 5).

A mercury drop experiment was also run in the attempt to ascertain the homogeneous nature of these systems (Table 6, entry 2). No significant difference in conversion was observed whether in the presence or absence of mercury (Table 3, entry 9), consistent with a homogenous process, that is proposed.

3. Mechanistic insights

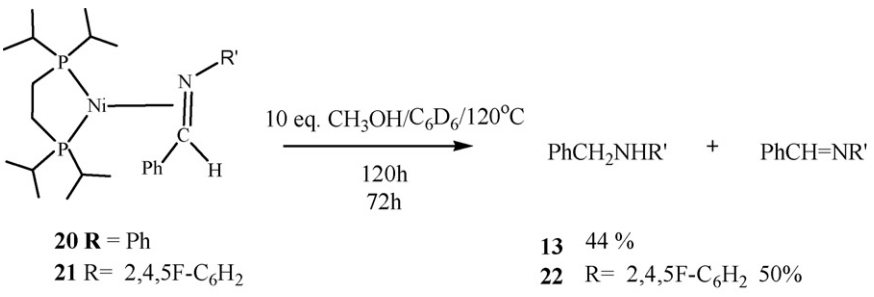
In order to provide some mechanistic insight and ascertained hydride source, as methanol is a hydrogen donor solvent, reaction with substrate **12** was run at atmospheric pressure (Table 5, entry 4). After a period of 24 h only a minimal amount of amine was formed (<10%). Benzaldehyde dimethyl acetal and free 2,3,4,5,6-pentafluoroaniline were detected by ^{1}H NMR (4.74 pm *s*, $-CH$) and GC–MS (M^+ 152, M^+ 183, respectively), along with **16** by ^{19}F NMR (Eq. (1)). The presence of the acetal can be explained in terms of a metal mediated nucleophilic addition of methanol to the imine moiety, thereby generating an α-amino ether [29]; a second addition of methanol likely to release free aniline and the solvolysis product, **18**. Longer reaction times gave full conversion



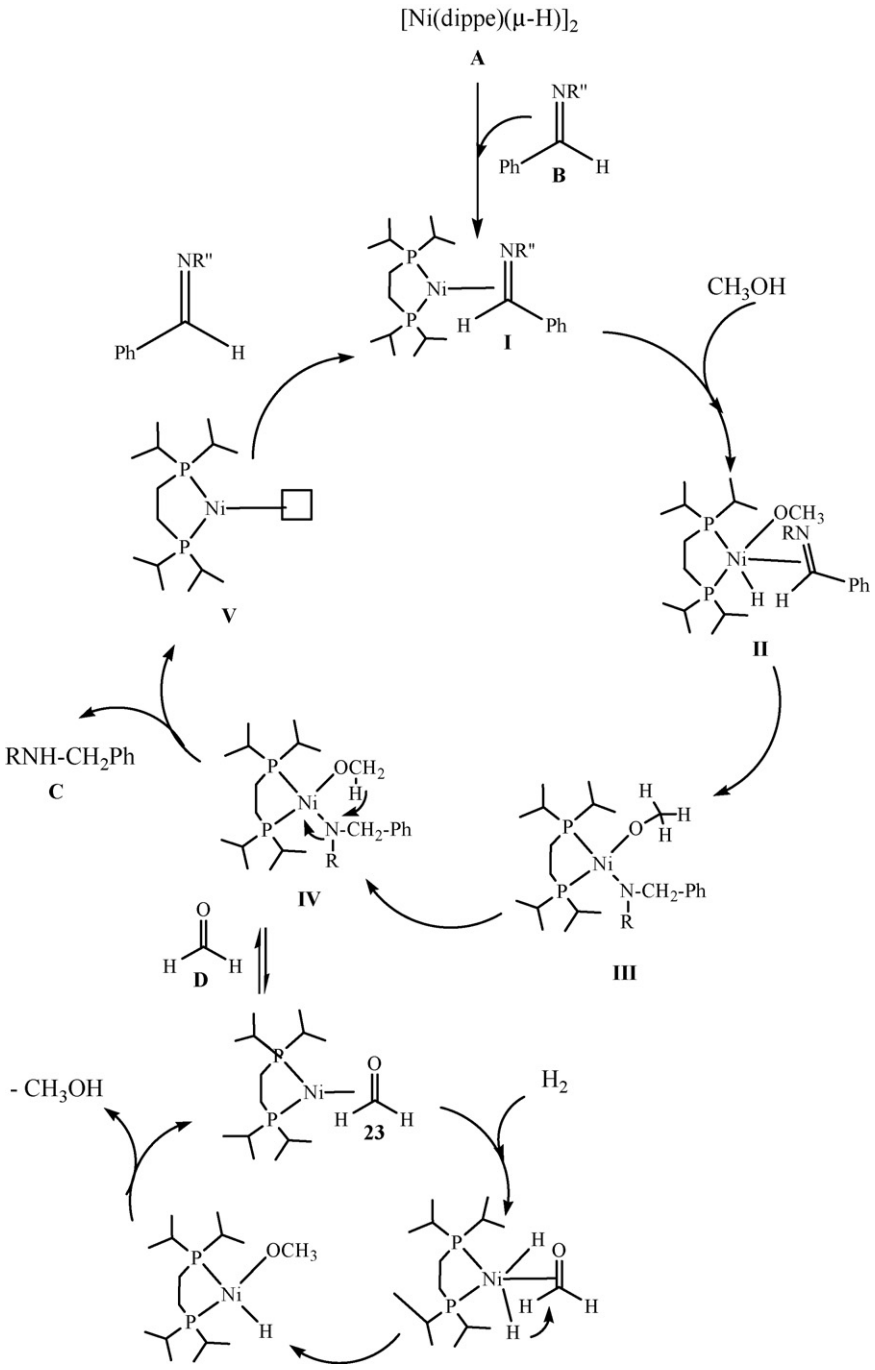
It is possible that a transfer hydrogenation process be undergone on this basis and in fact, in order to address this issue, stoichiometric reactions of η^2-C=N complexes **20** and **21** in the presence of excess methanol were run according to Scheme 2. Reactions were followed by ^{1}H and ^{31}P{^{1}H} NMR spectroscopy, in the interval of 100–120 °C: the disappearance of the signal attributed to the coordinated CH=N in the ^{1}H NMR spectrum, monitored therein [17]. The disappearance of signals due to methanol and the corresponding complex were confirmed at 120 °C, accompanied by the apparition of the signals corresponding to the amine at 3.99 ppm (*d J* 5.7 Hz, $-CH_2$) for **13** and 4.13 ppm (s, $-CH_2$) for $PhCH_2NH2,4,5F\text{-}C_6H_2$ **22** in the ^{1}H NMR spectrum. This premise was confirmed by a signal at 48.5 ppm (s, $-CH_2$) for **13** and 49.3 ppm (s, $-CH_2$) for 22 in the ^{13}C{^{1}H} NMR of the crude mixture. As seen in Scheme 2, although percent conversion to the amine are in the same range, reduction is faster with the electron poor imine even in the presence of a non-polar solvent [30].

Apparently, methanol is oxidized to formaldehyde as the imine is reduced in the process. This was confirmed by ^{13}C{^{1}H} NMR, a signal at 205 ppm (t, *J* 4.0 Hz) been found to appear within the spectrum. Additionally, for complex **21** the generation of gas pressure was observed in the NMR tube. The phosphorus signals of the η^2–*C,N* imine complexes [17] **20**–**21** disappeared in their corresponding ^{31}P{^{1}H}NMR spectra giving place to a major signal at 72.2 ppm in all of them, assigned to $[Ni_2(dippe)_2]$ [13,31].

Deuterium experiments were also performed in order to obtain better understanding of the reaction. A solution of complex **21** in CD_3OD was heated at 100 °C for 48 h; the conversion to amine **22**, confirmed by GC–MS apart from NMR. The incorporation of deuterium into the iminic carbon to yield the correspondingly deuterated amine, was followed by ^{13}C{^{1}H} NMR: the iminic carbon signal, a multiplet at 50.3 ppm, with $^2J_{C\text{–}D}$ = 21.3 Hz. Furthermore, a broad multiplet due to deuterium coupling was observed at 4.37 ppm in the ^{1}H NMR spectrum, the H/D exchange over the iminic proton resulting from the presence of CD_3OD, also confirmed by GC–MS. A multiplet centered at 47.5 ppm ($^2J_{C\text{–}D}$ 21.4 Hz, $-CD_2$) in the ^{13}C{^{1}H} NMR spectrum, corresponding to the deutero amine $PhCD_2ND2,4,5F\text{-}C_6H_2$, was also observed possibly due to C–H activation a subsequent coordination and hydrogenation of the deuterated imine being predicted on such basis [32].



Scheme 2.



Scheme 3. Suggested mechanism for the hydrogenation of imines.

A mechanism for hydrogenation of imines is proposed on the basis of the latter results (Scheme 3), inspired on previous reports concerning the use of a ruthenium(II) system for the hydrogen transfer from alcohols to ketones; a mechanism involving the formation of a dihydride *in situ* proposed therein [33], via a stepwise transfer of hydrogen from both the C—H and O—H bonds of methanol to the Ru center.

The *side on* coordination of the imine moiety to the catalytic precursor **A** in a first step [34], results in the formation of the nickel (0) intermediate **I**. This undergoes oxidative addition of methanol, yielding a Ni(II) – alcoxide-hydride intermediate **II** [35], the latter step proposed in analogy to the addition of R—O—H to other electron rich metals like Ru(0) and Ir(I) complexes [36]; the stabilization of the intermediate **II** by hydrogen bonding of solvent molecules to the lone pair of the bound nitrogen atom, proposed therein as an additional feature [8a,9].

The formation of an amido-alcoxide intermediate **III** is proposed to occur thereafter, a hydride transfer taking place over the iminic carbon, related complexes bearing amido or alcoxi groups with group 10 metals being well known [37]. The coordinated alcoxide is proposed to undergo β-elimination, followed by the elimination of the free amine **C**, and the concomitant formation of formaldehyde **D** [38] (which can in turn, remain bonded to Ni(0) center, see below) [9d,39], the β-elimination step supported on the basis of numerous reports [33,36,40]. Finally, the highly reactive 14e Ni(0) species **V** is proposed to

bind a new substrate molecule, thereby completing the catalytic cycle.

However, as seen before, reduction of imines with methanol as the *only* hydrogen donor is incomplete. Initially it was thought that catalyst poisoning ensued, as it does in other metallic systems where product inhibition is reported for hydrogenation of imines [3c,8b,27,41]. Thus, to prove or refute the latter, an independent reaction of amine **13** with **A** was undertaken, the results of which showed no binding of the amine to the [Ni(dippe)] fragment. No N—H activation products were detected either (see Section 5) and therefore, no catalyst poisoning was ensued in this manner.

Nevertheless, as observed in Scheme 3, the formation of an η^2-*C,O*-formaldehyde complex was proposed; the latter being explained by a displacement of substrate. This is inspired on a previous report using the otherwise similar Pt(0) complex $[Pt(PEt_3)_2(\eta^2\text{-}C,O\text{-}CH_2O)]$ [42], the existing evidence for the analogous nickel compound obtained in this work by reacting a stoichiometric amount of formaldehyde with the catalytic precursor $[Ni(dippe)(\mu\text{-}H)]_2$ at room temperature, the result of this experiment being the formation of complex **23**. In a similar experiment, imine **9** was added to the reaction mixture (see Section 5) resulting in the formation of $[(dippe)Ni(\eta^2\text{-}C,O\text{-}CH_2O)]$ and $[(dippe)Ni(\eta^2\text{-}C,N\text{-imine})]$ complexes in a ratio of 1:5, according to their corresponding $^{31}P\{^1H\}$ NMR signals at δ 80.1, 63.4 and 69.9, 65.8, respectively. The coordination of the η^2-*C,N* moiety is thereof proposed to be thermodynamically favored over the η^2-*C,O* at such conditions, but still competing for the available coordination sites in the [Ni(dippe)] fragment [43]. This in turn, may be a factor for the partial reduction of the imine where the sole hydrogen donor source is methanol.

To further address this question, the *in situ* hydrogenation of formaldehyde (parallel cycle already proposed in Scheme 3) was considered, provided that under the catalytic conditions used in a reactor vessel no formaldehyde was detected even though its formation was expected (*vide supra*) [44], therefore suggesting that either formaldehyde was being reduced back to methanol or else, no transfer hydrogenation was taking place. The hydrogenation of an authentic sample of formaldehyde under catalytic conditions using nickel was undertaken, the reaction run under 1 atm of H_2 pressure (see Section 5), at 100 °C during 90 min. A 60% conversion to methanol was detected after such time [45], Ni(II) oxidative addition products or formaldehyde detected under such conditions.

A proof for the hydrogen transfer step was then obtained under otherwise identical conditions; a catalytic run using complex **21** in neat CD_3OD, charging a vessel with 1 atm of H_2. Reduction was observed to occur firstly, a ratio of 0.25:1 amine/imine determined by ^1H NMR, after 24 h at 100 °C [46]. Interestingly, the signal for the residual proton resonance related to methanol decreased [47]; the formation of an acetal (^1H NMR, 5.35 ppm, *s*) with the concomitant generation of free 2,4,5-trifluoroaniline observed after 28 h, at 100 °C (monitored by GC–MS and ^{19}F NMR). Longer reaction times increased the amount of the acetal, a final 2.5/1/0.25 ratio of acetal/amine/imine determined by GC–MS. No signal was detected by ^1H NMR spectroscopy for the methoxy group of the acetal, in turn suggesting the incorporation of deuterium to the methoxy moiety [48]. In context, these results suggest that the reaction might proceed via the same type of hydrogen transfer mechanism; H_2 driving each reaction to completion [49]. It follows then, that in the absence of hydrogen pressure the formation of the acetal is favored, whereas in the presence of H_2 pressure the reductions of the imine and of formaldehyde to the corresponding amine and the regeneration of methanol, which are favored. For the sake of the argument, should the reduction process be undergone solely as a consequence of H_2 pressure, the residual methanol signal would have been expected to remain constant within the reaction follow up, which was not the case.

4. Conclusion

$[Ni(dippe)(\mu\text{-}H)]_2$ is an effective catalyst precursor for the hydrogenation of imines in methanol. The conversion is low in the presence of polar non-protic solvents like THF, and although transfer hydrogenation takes place under catalytic conditions, hydrogen pressure is badly needed to drive the reduction of the imine to completion, the formation of benzaldehyde dimethyl acetal resulting in the major product of solvolysis. In general, electron poor imines seem to be hydrogenated more rapidly than electron rich ones; the current work being to the best of our knowledge, the first report that evidences the participation and relevance of a η^2-intermediate in the hydrogenation of imines.

5. Experimental

All manipulations were carried out using standard Schlenk type and glove box techniques under argon (Praxair, 99.998), unless otherwise noted. Toluene and methanol were dried by standard methods and stored over 4 Å molecular sieves, under argon. THF was dried and distilled from deep purple solutions of sodium/benzophenone ketyl. *N*-phenyl-benzylamine and formaldehyde (37% solution) were purchased from Aldrich and were used as received. Deuterated solvents were purchased from Cambridge Isotope Laboratories and stored over 3 Å molecular sieves in an MBraun glove box (<1 ppm H_2O and O_2). $[Ni(dippe)(\mu\text{-}H)]_2$ was prepared following the general procedure reported in literature, using hexanes [50]. Imines were prepared as described elsewhere [51]. ^1H, $^{13}C\{^1H\}$, $^{31}P\{^1H\}$ and ^{19}F NMR spectra were recorded at room temperature on a 300 MHz Varian Unity spectrometer in $CDCl_3$, C_6D_6 or CD_3OD. ^1H and $^{13}C\{^1H\}$ NMR chemical shifts (δ, ppm) are reported relative to the residual proton and deuterium resonances of the deuterated solvent respectively, and all $^{31}P\{^1H\}$NMR spectra are reported relative to external 85% H_3PO_4, ^{19}F NMR chemical shifts were recorded relative to external standard CF_3COOH. Coupling constants (*J* values) are given in Hz. Compounds 14–24 were purified as described in the literature by column chromatography over neutral alumina, eluting with hexanes [52]. All NMR experiments were carried out using thin wall (0.38 cm) WILMAD NMR tubes with J. Young valves, heated in stirred silicon oil baths to the desired temperature, although acquired at room temperature. GC–MS determinations were performed using a Varian Saturn 3, equipped with a 30m DB-5MS capillary column.

5.1. Typical procedure for the hydrogenation of imines

Reactions were performed in a 300 mL Monel 400 Bench Top mini-reactor Parr, charged in the glove box. A typical experiment, exemplified for substrate **12**, is described as follows: substrate **12** (0.42 g, 1.55 mmol), $[Ni(dippe)(\mu\text{-}H)]_2$ (0.01 g, 0.015 mmol) and methanol (30 mL) were charged into the Parr reactor and closed under inert atmosphere. The reactor vessel (out of glove box) was purged with H_2; pressurized to 225 psi at r.t. and heated to the desired temperature under constant stirring. After 3 h, the reactor was allowed to cool down to room temperature and was depressurized in a fume hood. The vessel was opened to the air and an aliquot of the contained solution immediately injected into the GC–MS for analysis. Each experiment was run by triplicate, and the average conversion obtained was reported.

A typical workup was made as follows: Once the vessel was opened to the air the reaction mixture was filtered trough a frit with

neutral alumina and all volatiles evaporated in the vacuum line at room temperature. A yellow-orange oily residue was obtained for **16**, yield 0.401 g (95%). All other fluorinated amines were worked up similarly.

5.2. Mercury drop experiment

[Ni(dippe)(μ-H)]$_2$ (0.010 g, 0.016 mmol), substrate **9** (0.365 g, 1.55 mmol), and 30 mL of methanol were charged into a vessel, following the above described procedure; additionally adding two drops of elemental Hg to the reaction mixture. After reaction completion, the solution was filtered and analyzed by GC–MS: no significant difference in conversion between this experiment and the one in the absence of mercury been observed.

5.3. Stoichiometric experiments

To a solution of [Ni(dippe)(μ-H)]$_2$ (0.050 g, 0.078 mmol) in C_6D_6, the imine **1** (0.028 g, 0.16 mmol) was added and allowed to react until complete venting of H_2. Then, 10 equiv. (65 μL, 1.6 mmol) of dry methanol were added. The reaction was heated to the desired temperature (see Table 1) in an oil bath and monitored by ^{1}H and ^{31}P{^{1}H} NMR. After this time, the solution was filtered through a frit with neutral alumina and analyzed by GC–MS and ^{1}H NMR.

5.4. Catalytic experiment in CD_3OD.

An NMR tube equipped with a J. Young valve was charged with a solution of [Ni(dippe)(μ-H)]$_2$ (0.003 g, 0.005 mmol) in CD_3OD and imine 9 (0.109 g, 0.50 mmol) in the glovebox. The NMR tube was attached to a double line (vacuum/H_2), charged with hydrogen until saturation of H_2 (aproximately 45 min in acetone/dry ice bath). The tube was then closed and heated to 100 °C in a thermostated silicon oil bath. Disappearance of the η^2-coordinated imine complex as a result of reduction of the substrate was monitored by ^{1}H, ^{31}P{^{1}H} and ^{19}F NMR spectroscopies.

5.5. [Ni(dippe)(μ-H)]$_2$ stability assessment in methanol

To a dark red solution of [Ni(dippe)(μ-H)]$_2$ (0.020 g, 0.031 mmol) in C_6D_6, 10 equiv. of dry methanol (15 μL, 0.31 mmol) were added. The system was charged in an NMR tube following the procedure described above and heated to the desired temperature. Disappearance of [Ni(dippe)(μ-H)]$_2$ and appearance of decomposition products [13c] like [Ni(dippe)$_2$] and [Ni$_2$(dippe)$_2$] was followed by ^{31}P{^{1}H} NMR.

5.6. Competition experiment in stoichiometric conditions (imine\formaldehyde)

(a) *Stoichiometric formaldehyde*. To a solution of PhCH=N–{2,4,5-F-($C_6H_2F_3$)} (0.015 g, 0.062 mmol) in C_6D_6, was added formaldehyde (5 μL, 0.062 mmol) and 5 μL of toluene as an internal standard; the mixture monitored by ^{1}H and ^{19}F NMR. Then, to it was added [Ni(dippe)(μ-H)]$_2$ (0.020 g, 0.031 mmol), the formation of nickel complexes at r.t. assessed by ^{1}H, ^{31}P{^{1}H} and ^{19}F NMR spectroscopies.

(b) *Excess formaldehyde*. To a solution of [Ni(dippe)(μ-H)]$_2$ (0.020 g, 0.031 mmol) in C_6D_6, was added PhCH=N–{2,4,5-F-($C_6H_2F_3$)} (0.015 g, 0.062 mmol) and the mixture stirred until complete evolution of H_2. An excess of formaldehyde (25 μL, 0.31 mmol) was then added to the mixture, the progress of reaction monitored by ^{31}P{^{1}H} NMR.

5.7. Reaction of [Ni(dippe)(μ-H)]$_2$ with N-phenyl-benzyl-amine 13

To a solution of [Ni(dippe)(μ-H)]$_2$ (0.020 g, 0.031 mmol) in C_6D_6, was added $PhCH_2NHPh$ (0.011 g, 0.062 mmol). No reaction was observed among these two compounds at r.t. for 24 h nor by heating the mixture to 120 °C, only unreacted amine observed by ^{1}H NMR, along with small amounts of [Ni(dippe)$_2$].

5.8. Hydrogenation of formaldehyde

To a solution of [Ni(dippe)(μ-H)]$_2$ (0.010 g, 0.016 mmol) in C_6D_6, was added formaldehyde (0.046 g, 0.160 mmol) and 5 μL of toluene as an internal standard. The NMR tube with J. Young valve was charged with hydrogen in vacuum-line, following the procedure already described (*vide supra*) and the tube was heated to 100 °C in a thermostated oil bath. The disappearance of the η^2-coordinated complex was monitored by ^{31}P{^{1}H} NMR in C_6D_6. NMR spectra for [(dippe)Ni(η^2-*C,O*-CH_2O)] in C_6D_6, ^{1}H: δ (ppm): 5.28 (br, s), 4.20 (br, s), ^{31}P{^{1}H}: δ 80.1 (d, $^2J_{P-P}$ 59.2 Hz), 63.4 (d, $^2J_{P-P}$ 59.2 Hz).

5.8.1. Benzyl-(2,6-difluoro-phenyl)-amine

NMR spectra in $CDCl_3$, ^{1}H: δ (ppm) 7.45–7.58 (m, 5H), 7.30–7.37 (m, 1H), 6.99–7.12 (m, 2H), 4.53 (s, —CH_2), 3.98 (br s, —NH); ^{13}C{^{1}H}: δ (ppm) 153.6 (dd, $^1J_{C-F}$ 240.9, $^3J_{C-F}$ 7.5 *Hz),* 139.9, 129.2, 128.9, 127.7, 127.5, 117.9 (t, *J* 9.2 Hz), 100.7 (dd, $^2J_{C-F}$ 23.6, 4.4 Hz), 50.7 (t, *J* 4.3 Hz, —CH_2); ^{19}F: δ (ppm) −124.8 (t, $^3J_{F-H}$ 7.0 Hz, *2F*). MS (*m/z*, %), 219 (M, 100).

5.8.2. Benzyl-(2,3-difluoro-phenyl) amine

NMR spectra in $CDCl_3$, ^{1}H: δ (ppm) 7.57 (m, 5H), 7.09–7.12 (m, 1H), 6.84–6.98 (m, 2H), 4.40 (s, —CH_2), 4.50 (br s, —NH); ^{13}C{^{1}H}: δ (ppm) 151.0 (dd, $^1J_{C-F}$ 245.4, $^2J_{C-F}$ 36.5, Hz), 143.2 (dd, $^1J_{C-F}$ 241.9, $^2J_{C-F}$ 13.4 Hz), 138.6, 135.7, 128.7, 127.3, 107.5 (d, $^2J_{C-F}$ 2.2 Hz), 104.8 (t, *J* 17.6 Hz) 47.8 (s, —CH_2); ^{19}F: δ (ppm) −140.1 (m, 1F, *o*), −162.4 (m, 1F, *m*). Spectral data were found to be in accordance with those reported; see Ref. [52]. MS (*m/z*, %), 219 (M, 100).

5.8.3. Benzyl-(3,5-difluoro-phenyl)-amine

NMR spectra in $CDCl_3$, ^{1}H: δ (ppm) 7.18 (m, 5H), 5.93 (d *J* 8.1 Hz, 3H), 4.08 (s, —CH_2); ^{13}C{^{1}H}: δ (ppm) 164.2 (dd, $^1J_{C-F}$ 243.4, $^2J_{C-F}$ 15.8 Hz), 150.4 (t, $^2J_{C-F}$ 13.1 Hz), 138.4, 128.9, 127.7, 127.5, 95.6 (dd, $^2J_{C-F}$ 18.8, $^3J_{C-F}$ 9.5 Hz), 92.5 (t, *J* 26.2 Hz), 48.1 (s, CH_2); ^{19}F: δ (ppm) −110.7 (m, 2F). MS (*m/z*, %), 219 (M, 100).

5.8.4. Benzyl-(2,4,5-trifluoro-phenyl)-amine

NMR spectra in $CDCl_3$, ^{1}H: δ (ppm) 7.30–7.42 (m, 5H), 6.94 (m, 1H), 6.52 (m, 1H), 4.69 (d, *J* 5.7 Hz —CH_2), 4.36 (br s, —NH); ^{13}C{^{1}H}: δ (ppm) 128.9, 127.4, 104.7 (t, $^2J_{C-F}$ 22.2 Hz), 100.7 (dd, $^2J_{C-F}$ 23.6, 4.4 Hz), 48.1 (s, CH_2); ^{19}F: δ (ppm) −138.9 (d, $^3J_{F-H}$ *10.1* Hz, *o*), −142.7(t, $^3J_{F-H}$ 9.7 Hz, *m*). −151.4 (m, 1F, *p*). MS (*m/z*, %), 237 (M, 100).

5.8.5. Benzyl-(2,4,6-tetrafluoro-phenyl)-amine

NMR spectra in $CDCl_3$, ^{1}H: δ (ppm) 7.37 (m, 5H), 6.65 (t, *J* 6 Hz, 2H), 4.45 (s, —CH_2), 3.77 (br s, —NH); ^{13}C{^{1}H}: δ (ppm) 154.9 (d, $^1J_{C-F}$ 256.0 Hz), 153.6 (d, $^1J_{C-F}$ 238.3 Hz), 139.7, 128.8, 128.7, 128.1,127.8, 127.6, 100.4 (m), 51.2 (s, CH_2); ^{19}F: δ (ppm) −121.7 (d, $^3J_{F-H}$ *7.0* Hz, F, *p*), −125.4 (t, $^3J_{F-H}$ 8.2 Hz, *2F, o*). MS (*m/z*, %), 237 (M, 100).

5.8.6. Benzyl-(2,3,5,6-tetrafluoro-phenyl)-amine

NMR spectra in $CDCl_3$, ^{1}H: δ (ppm) 7.40–7.52 (m, 5H), 6.50 (m, 1H, *p*), 4.69 (d, *J* 5.7 Hz —CH_2), 4.36 (br s, —NH); ^{13}C{^{1}H}: δ (ppm) 146.7 (d, $^1J_{C-F}$ 244.6), 137.6 (d, $^1J_{C-F}$ 228.4), 137.6 (d, $^1J_{C-F}$ 228.2 Hz), 129.0, 128.9, 127.8, 127.6, 93.7 (t, $^2J_{C-F}$ 23.3 Hz), 49.9 (t,

4.4 Hz, —CH_2); ^{19}F: δ (ppm) −141.4 (m, 2F, *o*), −159.7 (t, $^3J_{F-H}$ 9.7 Hz, 2F, *m*). MS (*m/z*, %), 255 (M, 100).

5.8.7. Benzyl-(2,3,4,5,6-pentafluoro-phenyl)-amine

NMR spectra in $CDCl_3$, ^{1}H: δ (ppm) 7.30–7.35 (m, 5H), 4.48 (s, —CH_2), 3.91 (br s, —NH); ^{13}C{^{1}H}: δ (ppm) 144.6, 138.9, 129.0, 128.0, 127.8, 50.6 (t, *J* 4.2 Hz); ^{19}F: δ (ppm) −159.3 (d, $^3J_{F-F}$ 21.3 Hz, *m*), −164.8 (t, $^3J_{F-F}$ 19.9 Hz, *m*), −171.5 (tt, $^3J_{F-F}$ 21.8, 6.20 Hz, *m*). Spectral data were in accordance with those reported [10a]. MS (*m/z*, %), 273 (M, 100).

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.molcata.2008.10.003.

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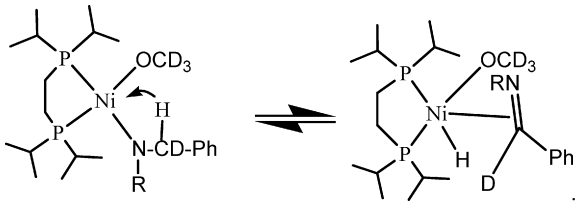

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[44] The volatiles from the catalytic reaction using **9** were bubbled into a NMR tube containing D_2O; the formation of methanol been corroborated by ^{1}H NMR.
[45] The hydrogenation of formaldehyde proceeded at apparently faster rate than that of the corresponding imine (*vide infra* main text), supporting the idea that it is the hydrogenation of formaldehyde that drives the reaction to completion and thus explains the absence of the former among resulting volatiles.
[46] The reaction was first monitored at room temperature for 21 h, yielding an 8% conversion to the amine. In contrast, the same reaction undergone at atm. pressure (Table 5, entry 4) resulted in <10% conversion to the amine; a slower rate, compared to the 25% conversion achieved at 100 °C after 24 h, using 1 atm of H_2 (yield determined against recovered unreacted imine). Additionally, the phosphorous signals for the (dippe)Ni(η^2-*C,O*-CH_2O) complex 23 were observed to disappear by $^{31}P\{^1H\}$ NMR, after heating to 100 °C.
[47] In the experiment monitored at room temperature, the solvent signals remain constant (with respect to imine) both $t = 0$ and $t = 21$ h; a decrease in the integrals of the methanol signals been observed after heating the reaction to 100 °C. The signal corresponding to the iminic proton decreased considerably after 48 h due to conversion to the acetal and reduction to the amine.
[48] The formation of the acetal was detected under catalytic conditions only, with pressures $\leq$1 atm of H_2. No solvolysis products were observed either in NMR tube experiments or using reactor vessels (stoichiometric amounts). *i.e.* the reaction of 21 in neat CD_3OD (see text) did not yield the acetal compound.
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