Synthetic Methods

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Acceptorless Dehydrogenation of Nitrogen Heterocycles with a Versatile Iridium Catalyst**

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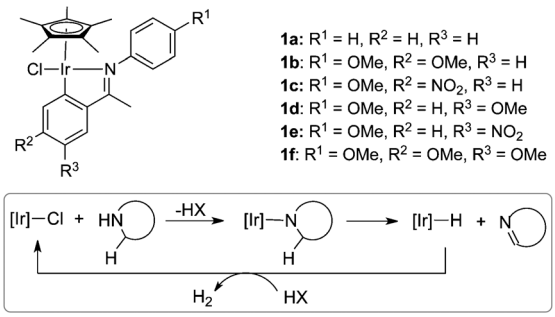
Dedicated to Professor Richard J. Puddephatt on the occasion of his 70th birthday

Catalytic dehydrogenation (CDH) is one of the most important reactions in the manufacturing of commodity chemicals.[1] For instance, annually approximately 17 million tons of styrene are produced by CDH of ethyl benzene. However, CDH has been much less used in the synthesis of fine chemicals, pharmaceuticals, and agrochemicals, although it offers considerable benefits with respect to atom economy and environmental impact because of the avoidance of stoichiometric oxidants. In recent years, CDH of alkanes, alcohols, and amines has been realized with metal complexes, although sacrificial hydrogen acceptors and additives are frequently used.[2] However, homogeneous catalysts capable of dehydrogenating heterocycles are very rare, and those catalysts that are active are mostly heterogeneous ones, which usually show poor functionality tolerance and require harsh reaction conditions.[3,4] More recently, Fujita and Yamaguchi reported the first example of homogeneous dehydrogenation of tetrahydroquinolines using a [Cp*Ir(2-hydroxypyridine)] catalyst.[5] A limitation is that only a few examples of 1,2,3,4-tetrahydroquinolines were demonstrated and the reaction conditions were relatively forcing [2 mol% catalyst for 20 h in refluxing *p*-xylene (bp 138°C) or 5 h in mesitylene (bp 165°C)]. Given the importance of nitrogen-containing aromatics in numerous naturally occurring alkaloids and synthetic pharmaceuticals, and as potential hydrogen storage materials,[6] developing a single catalytic system with higher CDH activity and wider scope would be of significant interest.

We recently reported that the cyclometalated [Cp*Ir^{III}]/imino complexes **1** are excellent catalysts for reductive amination (Scheme 1).[7] They readily form hydrides under H_2 pressure or when treated with formate, and could produce H_2 with the aid of an acid. Inspired by the Fujita work, we envisioned that when reacted with an amine, **1** could undergo



Scheme 1. Cyclometalated iridium complexes and hypothesized dehydrogenation of N-heterocycles.

β-hydrogen elimination, thus generating an imino bond and H_2 upon protonation.[8] It would be interesting to test if **1** could be exploited for the CDH of not only tetrahydroquinolines but other N-heterocycles as well.

We started the investigation choosing 2-methyl-1,2,3,4-tetrahydroquinoline (**2a**) as a model substrate. As expected, in the absence of a catalyst, formation of 2-methyl-quinoline (**3a**) was not detected in 2,2,2-trifluoroethanol (TFE; bp 78°C) after 2 h at reflux (Table 1, entry 1). After screening a variety of precatalysts and solvents (entries 2–19), we were pleased to observe that complex **1d**, which bears electron-donating OMe groups, did catalyze efficient CDH of **2a** in TFE, thus furnishing 88% conversion in 2 hours. Full conversion, along with release of H_2, was reached with 0.1 mol% overnight (entry 7).[9] Other complexes or solvents were less effective.

TFE appears to play multiple roles in the CDH. It may promote the dissociation of chloride from and hence the coordination of **2a** to **1d** before CDH takes place [Eq. (1)].[10]

$$[Ir]{-}Cl + CF_3CH_2OH \rightleftharpoons [Ir]^+ + Cl^-{\cdots}HOCH_2CF_3 \quad (1)$$

In support of this view, addition of a chloride salt inhibits the CDH (Table 1, entry 20). However, adding a silver or sodium salt did not improve the activity of **1d** when the reaction was carried out in toluene (entries 21 and 22). We noted that strong reflux is necessary for higher conversions, and remarkably, when nitrogen was bubbled through the solution, the CDH occurred even at room temperature, thus affording 52% conversion overnight. These observations indicate that the CDH is rate-limited by the step of dihydrogen formation,[8a,11] which we consider to be facilitated by TFE through protonation of the intermediate hydride [Eq. (2)].[12] Consis-

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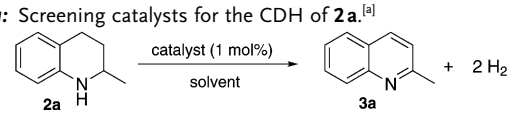
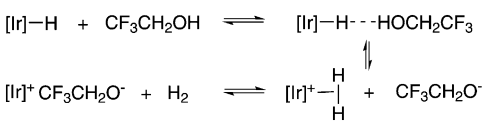
Table 1: Screening catalysts for the CDH of **2a**.[a]



Entry	Catalyst	Additive	Solvent	Conv. [%][b]
1[c]	none	–	TFE	n.r.
2	$[\{Cp^*IrCl_2\}_2]$	–	TFE	3
3	$IrCl_3 \cdot 3\,H_2O$	–	TFE	<1
4	**1a**	–	TFE	42
5	**1b**	–	TFE	74
6	**1c**	–	TFE	25
7[d]	**1d**	–	TFE	88
8	**1e**	–	TFE	29
9	**1f**	–	TFE	72
10	**1d**	–	DFE	23
11	**1d**	-	EtOH	4
12	**1d**	–	*i*PrOH	<1
13	**1d**	–	MeOH	14
14	**1d**	-	H_2O	3
15[c]	**1d**	–	THF	n.r.
16[c]	**1d**	–	DMF	n.r.
17	**1d**	–	MeCN	<1
18[c]	**1d**	–	toluene	n.r.
19[e]	**1d**	–	*p*-xylene	<1
20[f]	**1d**	TBAC	TFE	56
21	**1d**	$AgBF_4$	toluene	6
22[c]	**1d**	$NaBF_4$	toluene	n.r.

[a] Reaction conditions: **2a** (0.5 mmol) and catalyst (1 mol%) in solvent (3 mL) stirred at reflux under nitrogen for 2 h; 1 mol% additive when used. [b] Determined by NMR spectroscopy. [c] No reaction observed. [d] Full conversion with 0.1 mol% **1d** overnight. [e] **2a** (1.0 mmol) and catalyst (2 mol%), reflux, 20 h. [f] Used 20 mol% TBAC. Cp* = C_5Me_5, DFE = difluoroethanol, DMF = *N*,*N*-dimethylformamide, n.r. = no reaction, TBAC = tetrabutylammonium chloride, THF = tetrahydrofuran.

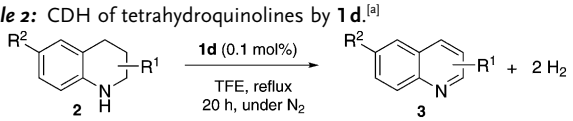
tent with this, the CDH became progressively slower when alcohols of lower acidity were used, for example, TFE (pK_a 12.5) versus 2,2-difluoro-ethanol (DFE; pK_a 13.1), and ethanol (pK_a 15.8; entries 7, 10, and 11). Thus, CDH by **1d** appears mechanistically distinct from that by the Fujita–Yamaguchi catalyst.[8,13]

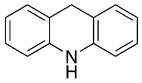
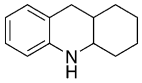
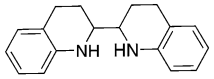


(2)

With the **1d**/TFE catalytic system in hand, we first subjected a variety of tetrahydroquinolines (**2**) to the CDH (Table 2). These were dehydrogenated to give quinolines generally in excellent yields with 0.1 mol% of **1d**. Lower yields were obtained with the nonsubstituted **2b** and 3-methyl-1,2,3,4-tetrahydroquinoline (**2c**), even at a higher catalyst loading of 1 mol% (entries 2 and 3).[14] All the 6-substituted substrates afforded high yields (entries 5–8), regardless of the nature of the substituent. The less basic **2j** was also dehydrogenated (entry 10). The acridine **3k** and the 1,2,3,4-tetrahydro variant **3l**, used as antitumor drugs and an analogue of acetylcholinesterase inhibitor,[15] were obtained from **2k** and **2l**, respectively, in good to excellent yields

Table 2: CDH of tetrahydroquinolines by **1d**.[a]



Entry	**2**	R^1	R^2	Yield [%][b]
1	**2a**	2-Me	H	95 (**3a**)
2[c]	**2b**	H	H	87 (**3b**)
3[c]	**2c**	3-Me	H	72 (**3c**)
4	**2d**	4-Me	H	87 (**3d**)
5	**2e**	2-Me	Me	94 (**3e**)
6	**2f**	2-Me	OMe	97 (**3f**)
7	**2g**	2-Me	F	93 (**3g**)
8	**2h**	2-Me	Cl	94 (**3h**)
9	**2i**	2-CH_2OH	H	81 (**3i**)
10	**2j**	2-Ph	H	92 (**3j**)
11	**2k**			92 (**3k**)
12	**2l**			88 (**3l**)
13[c]	**2m**			81 (**3m**)

[a] Reaction conditions: **2** (0.5 mmol) and **1d** (0.1 mol%) in TFE (3 mL) stirred at reflux under nitrogen for 20 h. [b] Yield of isolated product. [c] Used 1 mol% **1d**.

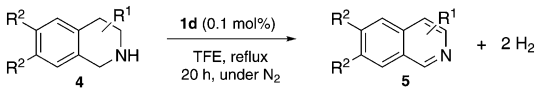
(entries 11 and 12). Notably, the 2,2′-biquinoline **3m**, a well-known diamine ligand, was generated along with liberation of 4 equivalents of H_2 from the octahydro form **2m** (entry 13). The catalyst is chemoselective, as seen in the CDH of **2i**, bearing a primary alcohol group, thus affording **3i** with exclusive selectivity towards the N-heterocyclic ring (entry 9).

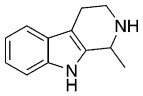
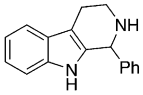
Isoquinolines and β-carbolines find broad pharmaceutical applications.[16] They can be obtained by traditional oxidation of the easily accessible tetrahydro or 3,4-dihydro analogues.[17] Following the CDH of **2**, we examined tetrahydroisoquinolines and tetrahydro-β-carbolines (**4**). These substrates are challenging to fully dehydrogenate, because of their tendency to form stable imine intermediates.[18] Table 3 shows that **4** can be dehydrogenated to isoquinolines (**5**) in good to excellent yields in general at a 0.1 mol% catalyst loading (entries 1–8). Among the substrates examined, only the nonsubstituted **4a** and sterically demanding **4e** necessitated a higher catalyst loading of 1 mol%. In the case of the former, **5a** was obtained in only 30% yield. Worth noting is that the tetrahydroharman **4i** was fully dehydrogenated to give the aribine **5i**, an important β-carboline (entry 9), and **4j** was converted into **5j** (entry 10) in high yield.

We next became interested in the CDH of 3,4-dihydroisoquinolines (**6**), which can be produced by the classical Bischler–Napieralski reaction (Table 4).[19] Although high yields were achieved, surprisingly a high catalyst loading (1 mol%) was required (entries 1–6). Under the reaction conditions used for **4** (Table 3), CDH of **6** was hardly detectable, thus suggesting that the reaction of **4** does not proceed via the intermediacy of **6**.

Apart from CDH, we found that **1d** also catalyzes the hydrogenation of **6a** into **4b** with excellent conversion at

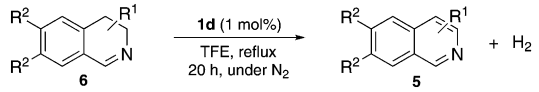
Table 3: CDH of tetrahydroisoquinolines and tetrahydro-β-carbolines by **1d**.[a]

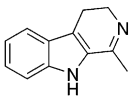


Entry	4	R^1	R^2	Yield [%][b]
1[c,d]	**4a**	H	H	30 (**5a**)
2	**4b**	1-Me	H	90 (**5b**)
3	**4c**	1-*i*Pr	H	92 (**5c**)
4	**4d**	3-Me	H	93 (**5d**)
5[c]	**4e**	1-*t*Bu	H	82 (**5e**)
6	**4f**	1-cyclohexyl	H	95 (**5f**)
7	**4g**	1-cyclohexyl	OMe	93 (**5g**)
8	**4h**	1-Ph	OMe	96 (**5h**)
9[c]	**4i**			93 (**5i**)
10	**4j**			95 (**5j**)

[a] The reaction conditions were the same as those in Table 2 except for using **4**. [b] Yield of isolated product. [c] 1 mol% **1d** used. [d] Yield as determined by NMR spectroscopy.

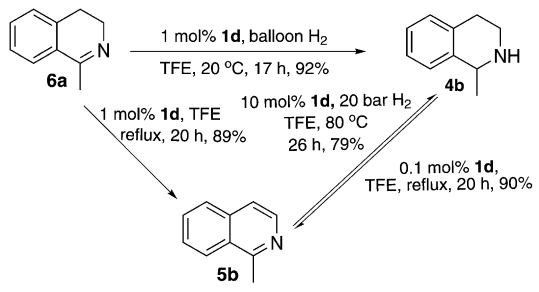
Table 4: CDH of 3,4-dihydroisoquinolines by **1d**.[a]



Entry	6	R^1	R^2	Yield [%][b]
1	**6a**	1-Me	H	89 (**5b**)
2	**6b**	1-*i*Pr	H	92 (**5c**)
3	**6c**	1-cyclohexyl	H	93 (**5f**)
4	**6d**	1-cyclohexyl	OMe	94 (**5g**)
5	**6e**	1-Ph	OMe	95 (**5h**)
6	**6f**			81 (**5i**)

[a] The reaction conditions were the same as those in Table 2 except for using **6** and 1 mol% **1d**. [b] Yield of isolated product.

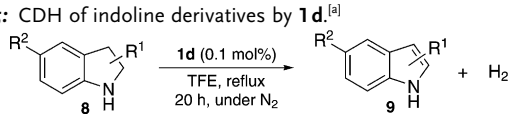
20 °C and 1 atm H_2 pressure (Scheme 2). The highly stable **5b** was hydrogenated as well, although more forcing reaction conditions were needed. Together with the results in Tables 3 and 4, these results weave a unique network which links the three forms of isoquinoline by hydrogenation and dehydrogenation using a single catalyst (**1d**; Scheme 2).



Scheme 2. Hydrogenation/dehydrogenation-linked interchangeable transformations between isoquinoline and derivatives.

Bearing in mind that there are diverse ways for the preparation of indolines,[20] direct CDH adds a valuable alternative to the strategies of indole synthesis. Using **1d**, various indoline derivatives could be dehydrogenated, thus affording indoles in excellent yields (Table 5). In particular, sterically demanding 2,3-dimethyl- and 2-phenylindolines were dehydrogenated to indoles in 96% yield (entries 5 and 7). However, as with **4a**, the nonsubstituted **8a** was more difficult to dehydrogenate.

Table 5: CDH of indoline derivatives by **1d**.[a]

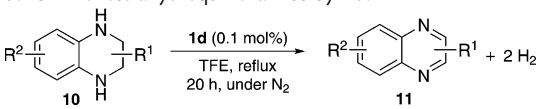


Entry	8	R^1	R^2	Yield [%][b]
1[c]	**8a**	H	H	91 (**9a**)
2	**8b**	H	OMe	95 (**9b**)
3[d]	**8c**	H	Cl	93 (**9c**)
4	**8d**	2-Me	H	90 (**9d**)
5	**8e**	2-Me, 3-Me	H	96 (**9e**)
6	**8f**	3-Me	H	98 (**9f**)
7	**8g**	2-Ph	H	96 (**9g**)

[a] The reaction conditions were the same as those in Table 2 except for using **8**. [b] Yield of the isolated product. [c] Used 1 mol% **1d**. [d] Used 0.5 mol% **1d**.

Traditional synthesis of quinoxalines makes use of reactions such as condensation and oxidative cyclization.[21] CDH is not known for this. We therefore investigated the dehydrogenation of tetrahydroquinoxalines (**10**; Table 6). The CDH worked, giving rise to good to excellent yields of the quinoxalines **11** with 0.1 mol% of **1d**. However, a higher catalyst loading was necessary for the sterically bulky **10d** and **10e**.

Table 6: CDH of tetrahydroquinoxalines by **1d**.[a]

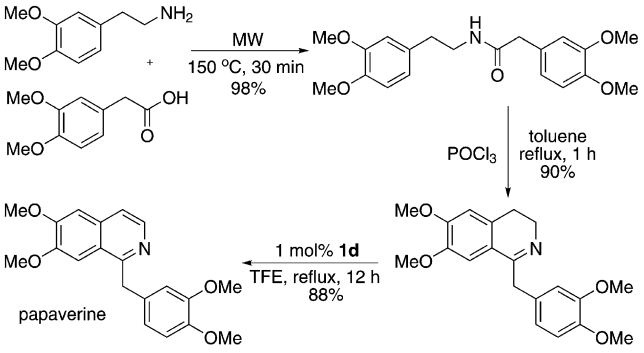


Entry	10	R^1	R^2	Yield [%][b]
1	**10a**	2-Me	H	92 (**11a**)
2	**10b**	2-Ph	H	79 (**11b**)
3	**10c**	2-Me, 3-Me	H	93 (**11c**)
4[c]	**10d**	2-Me, 3-Ph	H	85 (**11d**)
5[c]	**10e**	2-Ph, 3-Ph	H	82 (**11e**)
6	**10f**	H	5-Me	62 (**11f**)
7	**10g**	H	6-Me	64 (**11g**)

[a] The reaction conditions were the same as those in Table 2 except for using **10**. [b] Yield of the isolated product. [c] Used 1 mol% **1d**.

To showcase the synthetic utility of the CDH, we applied the protocol to a rapid total synthesis of two well-known alkaloids, papaverine and harmine. Papaverine is an opium alkaloid antispasmodic drug, clinically used for the treatment of vasospasm and occasionally for erectile dysfunction.[22]

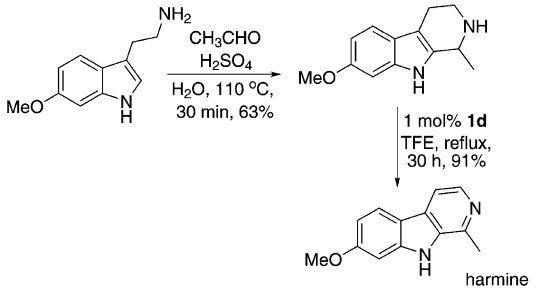
Harmine is a major β-carboline alkaloid found in *pegunam harmala* extract. It is an inhibitor of monoamine reuptake system and has also shown cytotoxic activities against a series of tumor cell lines.[23] Our synthesis of papaverine started with the condensation of homoveratric acid and homoveratrylamine under microwave-assisted, neat conditions, thus generating the corresponding amide in almost quantitative yield (Scheme 3). The amide was then treated with $POCl_3$ to



Scheme 3. Synthesis of papaverine by CDH. MW = microwave.

furnish a cyclic imine by the Bischler–Napieralski reaction.[19] The last step of the synthesis was accomplished by **1d**-catalyzed CDH of the 3,4-dihydroisoquinoline (see the Supporting Information for details). The three-step synthesis, employing commercially available materials with an overall yield of 78%, appears to offer a most efficient and economically sound method for this significant alkaloid.[24]

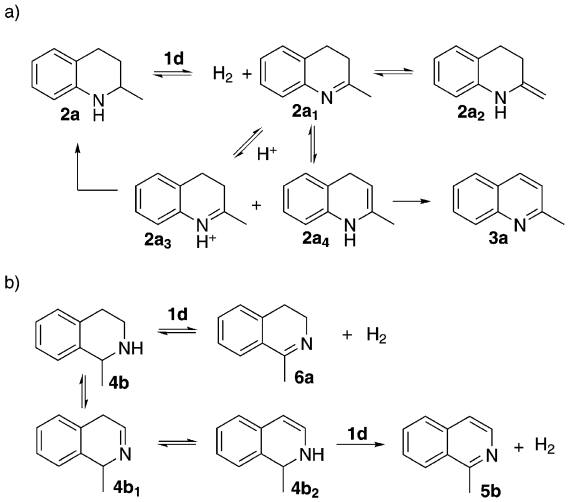
Scheme 4 shows the synthesis of harmine starting with a Pictet–Spengler reaction[19] of acetaldehyde with 6-methoxytryptamine. CDH of the resulting tetrahydroharmin by **1d** afforded the target alkaloid, with an overall yield of



Scheme 4. Synthesis of harmine by CDH.

57% (see the Supporting Information for details). In comparison with other known methods,[25] this concise synthesis of harmine using commercially available materials is high-yielding and less wasteful under mild reaction conditions.

Preliminary mechanistic studies of CDH of **2a** and **4b** shed light on how these CDH reactions may take place (see the Supporting Information for details). In the presence of **1d** in [D_3]TFE, **2a** undergoes rapid H–D exchange at the C2-position at room temperature.[26] However, no other species were observed apart from **2a** and trace amounts of **3a** in the ^{1}H NMR spectrum. Under the normal refluxing conditions (Table 2), **3a** was obtained with deuterium incorporation at the C3 and methyl position. On this basis, CDH of **2a** is suggested to proceed by the pathway shown in Scheme 5a. At



Scheme 5. Proposed pathways for the CDH of tetrahydroquinolines, and tetrahydro- and dihydroisoquinolines.

low temperature, **2a** is in equilibrium with $\mathbf{2a_1}$, which is probably protonated by or hydrogen-bonded with the medium, and $\mathbf{2a_2}$, with the equilibrium strongly favoring **2a**. At high temperature $\mathbf{2a_1}$ isomerizes to $\mathbf{2a_4}$ by acid catalysis, which hydrogenates $\mathbf{2a_3}$, thus resulting in the formation of **3a** and **2a**.

When **4b** was subjected to CDH with 0.1 mol% of **1d** in refluxing TFE for a short time, both **6a** and **5b** were observed. However, **6a** showed no observable CDH under these reaction conditions, although it gave **4b** and **5b** at 1 mol% of **1d**. In contrast, using of 0.1 mol% of **1d** but in the presence of **4c** (Table 3), **6a** was converted into **4b** and **5b**, thus showing that **6a** can readily undergo CDH, probably by **4b**, if a hydride donor such as **4c** is present. These observations suggest that the CDH of **4b** involves a pathway as shown in Scheme 5b, where **4b** can be dehydrogenated into either **6a** or $\mathbf{4b_1}$. But it is $\mathbf{4b_1}$ which gives rise to the product **5b**. The formation of **5b** from **6a** proceeds by its first reduction to **4b**. When **6a** alone is dehydrogenated, it is likely to be reduced to **4b** in the first place by TFE,[27] a solvent of well-known resistance to oxidation. This explains why **6** is more difficult to reduce than **4**.

In summary, we have developed a versatile catalyst for the oxidant-free, acceptorless CDH of various benzofused N-heterocycles. The high activity and broad substrate scope of the catalytic system make the protocol a promising alternative for laboratory and industrial applications, and this is reinforced by the ease of operation, atom economy, and environmental benefits offered by CDH.

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[4] Apart from a few examples of hydroquinolines CDH (Ref. [5]), only three indolines have been repoted to undergo homogeneous CDH: a) Y. Tsuji, S. Kotachi, K. T. Huh, Y. Watanabe, *J. Org. Chem.* **1990**, *55*, 580; b) S. M. Lu, Y. Q. Wang, X. W. Han, Y. G. Zhou, *Chin. J. Catal.* **2005**, *26*, 287.

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[8] However, **1** differs from the Fujita–Yamaguchi catalyst not only structurally but also probably mechanistically. Containing no bifunctional ligand, the hydride generated from **1** can only be protonated intermolecularly. In contrast, [Cp*Ir(2-hydroxypyridine)] operates by ligand-promoted dehydrogenation: a) K. Fujita, N. Tanino, R. Yamaguchi, *Org. Lett.* **2007**, *9*, 109; b) H. Li, J. Jiang, G. Lu, F. Huang, Z. X. Wang, *Organometallics* **2011**, *30*, 3131.

[9] Formation of H_2 was confirmed by GC analysis and quantified with the water displacement method. Please see the Supporting Information for details.

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[11] In line with dihydrogen formation being turnover-limiting, Ir-H was observed in the ^{1}H NMR spectrum at RT, 5 min after mixing **2a** with **1d** (1 mol%) in TFE in a NMR tube, along with ca. 4% of **3a**.

[12] TFE can hydrogen bond with and protonate metal hydrides, thus forming M-(H_2): a) 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. J.* **2003**, *9*, 2219; b) M. Besora, A. Lledós, F. Maseras, *Chem. Soc. Rev.* **2009**, *38*, 957.

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[26] This suggests again that dehydogenation, without releasing H_2, is a fast process. Also see Ref. [11].

[27] When **1d** was heated in TFE at 60 °C, an Ir-H hydride resonance was observed at $\delta = -10.10$ ppm along with trifluoroacetaldehyde in the ^{1}H NMR spectrum (see the Supporting Information).

