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Iridium-Catalyzed Acid-Assisted Hydrogenation of Oximes to Hydroxylamines

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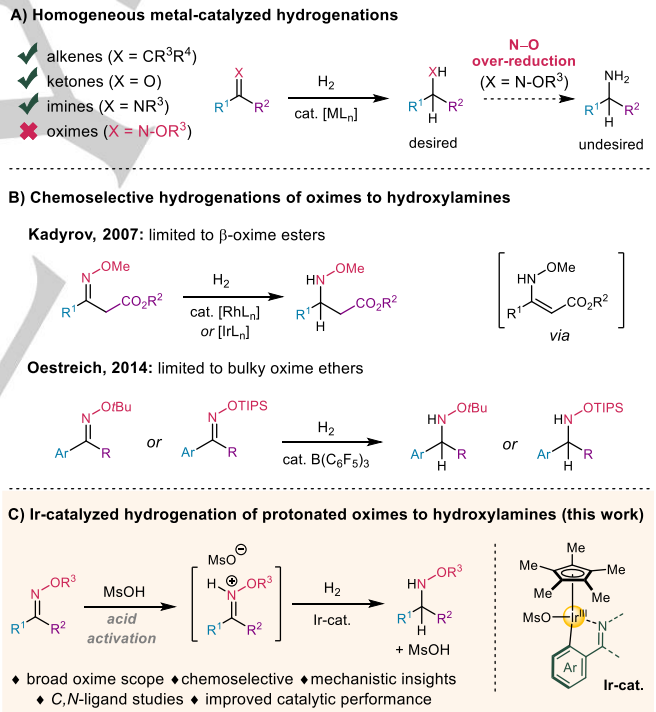
Abstract: We found that cyclometalated cyclopentadienyl iridium(III) complexes are uniquely efficient catalysts in homogeneous hydrogenation of oximes to hydroxylamine products. A stable iridium *C,N*-chelation is crucial, with alkoxy-substituted aryl ketimine ligands providing the best catalytic performance. Several Ir-complexes were mapped by X-ray crystal analysis in order to collect steric parameters that might guide a rational design of even more active catalysts. A broad range of oximes and oxime ethers were activated with stoichiometric amounts of methanesulfonic acid and reduced at room temperature, remarkably without cleavage of the fragile N-O bond. The exquisite functional group compatibility of our hydrogenation system was further demonstrated by additive tests. Experimental mechanistic investigations support an ionic hydrogenation platform, and suggest a role for the Brønsted acid beyond a proton source. Our studies provide deep understanding of this novel acidic hydrogenation and may facilitate its improvement and application to other challenging substrates.

Introduction

The catalytic hydrogenation using homogeneous metal catalysts is among the most important transformations in organic synthesis.[1] At industrial level, it became the cornerstone of sustainable manufacturing for both bulk and fine chemical intermediates.[2] Those include, for example, unsaturated alkene, ketone and imine functionalities which are reduced to their corresponding saturated products (Scheme 1A).[3] The use of widely available hydrogen gas as cost-efficient reductant and typically low catalyst loadings render this process economical and efficient. In this regard, the development of enabling catalysts, most frequently represented by phosphine-ligated late transition-metals (e.g. Rh, Ru, Ir, Pd), has been crucial.[4] However, several ubiquitous functional groups, like oximes, remain refractory to hydrogenation using typical homogeneous catalysts. Oxime substrates are less reactive, and when reactivity is observed, over-reduction by cleavage of the rather labile N–O bond produces primary amine products instead of hydroxyl amines.[5] This is in many instances not desirable, as the hydroxylamine motif is valuable and present in many pharmaceuticals, agrochemicals, as well as natural products.[6] Additionally hydroxylamine derivatives are versatile synthetic intermediates,[6c,7a-c] powerful ligands[7d,e] and catalysts.[7f]



Scheme 1. Catalytic homogeneous hydrogenations of oximes to hydroxylamine products.

Hence, a generally applicable synthesis of *N*-alkyl-*N*-hydroxylamines *via* a catalytic chemoselective oxime hydrogenation is highly desirable. To the best of our knowledge, the two reported methods describing such a process, are both limited regarding the oxime substrate substitution pattern (Scheme 1B). In 2007, Kadyrov et al. reported a homogeneous hydrogenation of β-oxime esters employing phosphine rhodium and iridium catalysts under high pressure of hydrogen gas.[8] This substrate type easily tautomerizes to 2,3-unsaturated esters,

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therefore the described oxime hydrogenation reaction may be more appropriately described as a C=C double bond reduction. In 2014, Oestreich *et al.* disclosed a FLP-catalyzed hydrogenation of oxime derivatives using a tris(pentafluorophenyl)borane catalyst.[9] This method is limited to oxime ethers bearing very bulky O-substituents (*t*Bu or Si(*i*Pr)$_3$) and requires high catalyst loading of 5-10 mol%.

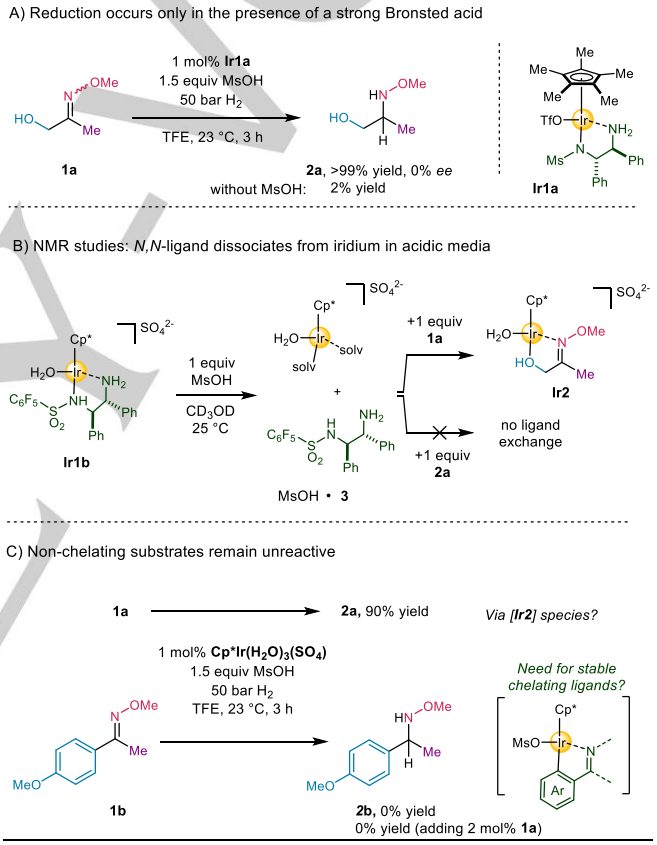
Very recently, we disclosed the development of cyclometalated Cp^{X}Ir(III) methanesulfonate complexes, and demonstrated their efficiency in unique enantioselective hydrogenations of oximes to hydroxylamines under acidic conditions.[10a,b] Herein we present a full account on these developments leading to the discovery of an active hydrogenation catalyst (Scheme 1C). Several novel catalyst derivatives are disclosed and compared in terms of their catalytic efficiency. In addition, we include an extended oxime substrate scope, further expanding the generality of the method. Finally, some insights on the reaction mechanism are provided in order to foster understanding of this concept of "acid-assisted ionic hydrogenation" with the goal to facilitate its application to other classes of challenging substrates.

Results and Discussion

Our efforts were initiated by the hydrogenation of β-hydroxyl acetone oxime ether **1a** (a mixture of *E* and *Z* isomers) to access 2-(methoxyamino)propan-1-ol (**2a**)[10d] (Scheme 2A). Considering the complete lack of activity and selectivity of several conventional catalysts (Rh, Ru, Ir, Pt with phosphorous-based ligands) toward oxime hydrogenation,[10c] we took inspiration in successful heterogeneous variants using Pt/H$_2$ with super-stoichiometric amounts of acid.[11] We hypothesized that activation of the oxime substrate by protonation could be essential for reactivity. Due to the low basicity of oximes with a pKa that is approximately 5 units lower than the one of imines,[12a-c] a much stronger Brønsted acid would be required for protonation. Moreover, the strongly acidic conditions would prevent the nitrogen lone pair of the formed hydroxyl amine from coordination and eventually poisoning the transition metal catalyst.

We turned our attention to Cp*Ir(III) diamine complexes, exemplified by **Ir1a**, which were previously successful for ketone and imine hydrogenations in acidic media.[13] Pleasingly, treating **1a** with 1 mol% of **Ir1a**, 1.5 equivalents of methanesulfonic acid (MsOH) and 50 bar of H$_2$ pressure in trifluoroethanol (TFE) afforded desired methoxyamine **2a** in quantitative yield at room temperature (Scheme 2A). In stark contrast, only trace amounts of **2a** were detected in the absence of MsOH. In fact, at least stoichiometric amounts of acid with respect to the oxime substrate is required for complete conversion (*vide infra*). A striking observation was the lack of any enantioselectivity in the reaction. This prompted us to investigate the role of the chiral *N,N*-diamine ligand. We thus conducted stoichiometric proton and ^{19}F-NMR studies in CD$_3$OD using complex **Ir1b**,[13d] bearing a fluorinated sulfonamide moiety as beacon (Scheme 2B) (see SI for full details). After addition of one equivalent of MsOH, partial dissociation of diamine ligand **3** from the iridium center was observed. Decomposition of **Ir1b** was further enhanced upon addition of one equivalent of β-hydroxyl oxime substrate **1a**, presumably forming the *N,O*-ligated complex **Ir2**. No similar ligand exchange was detected with one equivalent of **2a** instead, which seemed to be a less competent ligand than **1a**.

The dissociation of the diamine ligand of **Ir1a** or **Ir1b** should be further enhanced during catalysis (significantly higher concentration of acid relative to the iridium catalyst). In fact, conducting the reduction of **1a** with 1 mol% of 'naked' Cp*Ir(H$_2$O)$_3$(SO$_4$) complex afforded **2a** in 90% yield (Scheme 2C). The substrate ability of *in situ* chelation to iridium forming **Ir2** seemed relevant. For instance, no reduced product **2b** was detected when acetophenone-derived oxime *E*-**1b** lacking the *β*-hydroxyl group was subjected to identical hydrogenation conditions. As well, adding catalytic amounts of **1a** as ligand proved ineffective. Having the aim to generalize the reduction of oxime substrates without additional coordinating groups, we decided to further investigate the importance of iridium chelation with auxiliary ligands.



Scheme 2. Preliminary catalyst identification and reactivity studies. General conditions: 2 mmol **1**, 3 mmol MsOH, 20 µmol [**Ir**] in TFE (2 mL) at 23 °C for 3 h; yield of **2** determined by ^{1}H-NMR using 1,3,5-trimethoxybenzene as internal standard, and equals the conversion of the oxime starting material.

Synthesis of the catalyst library

Concerning the design aspects, we targeted half sandwich Ir(III) complexes having a stable capping Cp* ligand, a lower aryl ketimine *C,N*-chelating unit, and a displaceable (pseudo)halide ligand (Scheme 3). These well-defined iridacycles have been shown by Xiao and others to be effective catalysts for related imine hydrogenation, other catalytic hydrogenations, dehydrogenation reactions, oxidations, and hydro-functionalization reactions.[14] To test them towards oxime hydrogenations, a series of complexes **Ir4a-Ir4h** were prepared by cyclometalation of different iminoarenes **4a-4h** with [Cp*IrCl$_2$]$_2$, using a slightly modified version of the method originally reported

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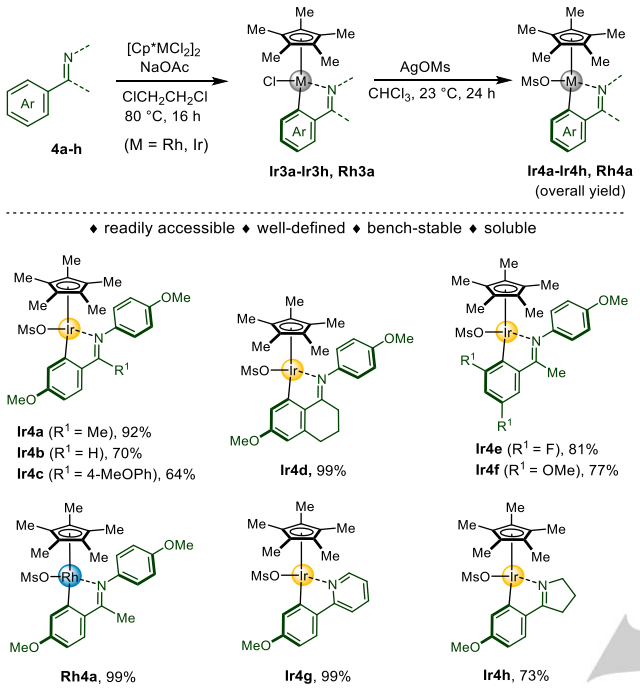
by Davies.[15a,b] In a second step, methanesulfonate containing derivatives **Ir4a-Ir4h** were accessed from **Ir3a-Ir3h** by salt metathesis with silver methanesulfonate. Conveniently, all shown high oxidation state 18-electron iridium(III) complexes were stable to air and moisture, hence their handling and storage does not require the use of sophisticated equipment.

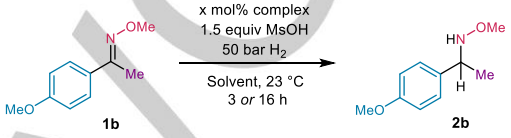


Scheme 3. General synthesis of the cyclometalated Cp*M(III) complexes (M = Rh, Ir) used for this study. Overall isolated yields are shown for each complex.

Reaction development and structure-performance relationship studies of the C,N-ligands

Continuing with our studies towards the reduction of oxime *E*-**1b**, we investigated cyclometalated Cp*Ir(III) complexes **Ir4** as catalysts in the transformation (Table 1). Previous studies regarding imine hydrogenations had shown that complexes bearing alkoxy-substituted aryl ketimine chelates, such as the *p*-methoxyacetophenone-derived **4a**, displayed the best activities.[14c,e] To our delight, **2b** was quantitatively formed after exposure of **1b** to 1 mol% of **Ir4a**, 1.5 equivalents of MsOH and 50 bar of H_2 pressure in TFE as solvent (entry 1). Most remarkably, the transformation proceeded without detectable cleavage of the N-O bond. Having identified a performing catalyst class, other solvents were tested in the reaction. At an even lower 0.5 mol% catalyst loading, a quantitative yield of **2b** was maintained in cheaper and more sustainable *i*PrOH, (entries 2 and 3). Aprotic solvents, such as 2-MeTHF, toluene, or dimethyl carbonate, are also suitable, reaching excellent levels of reactivity (>90% yield) (entries 4-6). Nevertheless, simple alcoholic solvents are in general superior. Using as low as 0.1 mol% of **Ir4a** in *i*PrOH afforded **2b** in 45 % yield (450 TON) (entry 7). This reaction set-up was considered optimal for testing and comparing the catalytic efficiency of different complexes **Ir4a-Ir4h**. The results are summarized in entries 8-14 of Table 1. To gain insights into the ligand structure-performance relationship, stereoelectronic modifications were performed at three different subunits of the aryl-imine ligand architecture: 1) the pendant imine *C*-substituent; 2) the *N*-donor functionality; 3) the metalated aromatic ring. Regarding the pendant imine *C*-substituent, removal of the methyl substituent of **Ir4a** to generate *p*-methoxybenzaldehyde derivative **Ir4b** is detrimental (entries 7 vs 8). In contrast, **Ir4c** featuring a novel benzophenone-derived scaffold performed better (entries 7 vs 9). We rationalize this by the increased stability of the higher substituted ketimine ligands. The geometry of their chelate (e.g. bite angle) appeared to have less impact in catalytic performance. For instance, **Ir4d** having a more rigid cyclic tetralone-derived backbone displayed marginally superior activity than **Ir4a** (entries 7 vs 10). Therefore, the simpler acetophenone backbone of the later was deemed as the best compromise for subsequent studies.

Table 1. Reaction optimization and catalyst screening studies.[a]



Entry	Complex	mol% Cat.	Solvent	% Yield[b]
1	**Ir4a**	1.0	TFE	>99
2	**Ir4a**	1.0	*i*PrOH	>99
3	**Ir4a**	0.5	*i*PrOH	>99
4	**Ir4a**	0.5	2-MeTHF	91
5	**Ir4a**	0.5	toluene	95
6	**Ir4a**	0.5	$OC(OMe)_2$	97
7	**Ir4a**	0.1	*i*PrOH	45
8	**Ir4b**	0.1	*i*PrOH	13
9	**Ir4c**	0.1	*i*PrOH	61
10	**Ir4d**	0.1	*i*PrOH	48
11	**Ir4e**	0.1	*i*PrOH	32
12	**Ir4f**	0.1	*i*PrOH	55
13	**Ir4g**	0.1	*i*PrOH	61
14	**Ir4h**	0.1	*i*PrOH	28
15	**Rh4a**	1.0	*i*PrOH	<5

[a] Conditions: 0.30 mmol **1**, 0.45 mmol MsOH, indicated loading of **complex** in solvent (0.3 mL) at 23 °C for 3 h (entries 1-6) or 16 h (entries 7-14); [b] yield determined by ^{1}H-NMR using 1,3,5-trimethoxybenzene as internal standard, being equal to the conversion of the oxime starting material unless otherwise stated.

The stereoelectronic properties of the metalated aromatic ring are expected to have a major impact on the catalyst performance, in terms of iridacycle stability and Ir-hydride nucleophilicity.[15d] In our preceding publication we found that *ortho* alkoxy substituents had a positive influence.[10a] Alkoxy and fluoro groups placed *ortho* to the metalated carbon may provide extra stabilization to the carbon-metal bond.[16] Being aware that *ortho*-alkoxy acetophenone-derived ligands present regioselectivity issues in their complexation to iridium,[14e,15b] we explored **Ir4f** having a

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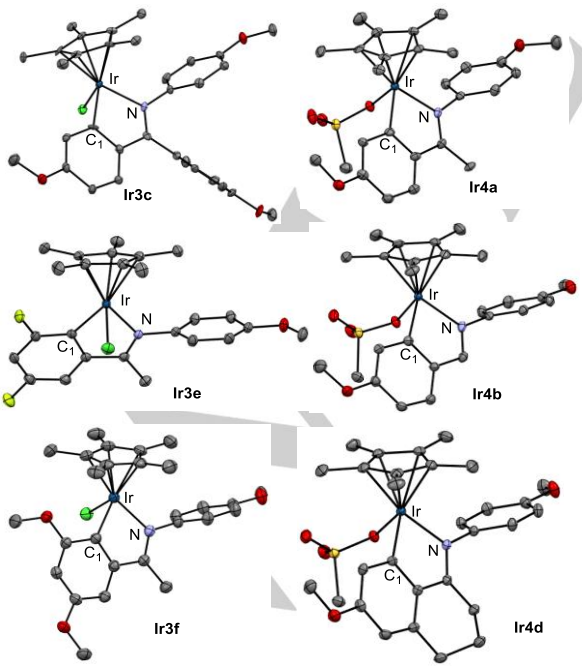
symmetrical 3,5-dimethoxy substitution. Pleasingly, it showed improved catalytic activity compared to the 4-methoxy analogue **Ir4a** (entries 7 vs12). In contrast, the 3,5-difluoro derivative **Ir4e** was less efficient (entries 11 vs 12). Some variations of the privileged *N*-aryl imine ligand moiety[14a] were also feasible. For instance, complex **Ir4g** bearing a 2-aryl pyridine ligand outperformed the *N*-aryl ketimine-derived standard **Ir4a** (entries 7 vs 13). The dihydropyrrole analogue **Ir4h** was as well active (entries 7 vs. 14), opening new possibilities for *C,N*-ligand design. Related rhodium complexes are also known to engage in hydrogenations.[17] However, rhodacycle **Rh4a** was totally ineffective towards the reduction of **1b** (entry 15). Presumably, cyclometalated Cp*Rh(III) complexes are less stable than their iridium congeners towards proto-demetallation due to the weaker Rh-carbon bond.[18a] Additionally, Cp*Rh(III) hydrides may be more prone to decompose via reductive elimination processes.[18b-e]

Solid state structure and key parameters for the iridium complexes

We obtained X-ray quality single crystals for a variety of chloride complexes **Ir3** and methanesulfonates **Ir4** by slow diffusion of a nonsolvent to the respective solutions of the iridium complexes at ambient temperature (see SI for experimental details). X-Ray crystallographic analysis provided insights into their molecular geometry in the solid state and selected parameters were compared (Figure 1). All feature a 'piano-stool' shape with a distorted pseudo-tetrahedral geometry around the iridium center and are in full accordance with related Ir-complexes.[15a-c] Despite different electronic and substitution pattern of the chelating C,N-ligand, only very small differences in the bond distances C1-Ir, N-Ir and angles are observed. Nevertheless, the systematic collection of the complexes structural parameters might set the basis for a correlation to their reactivity. Our studies may serve as a guide for the development of even more active iridium complexes in the future.



Complex	$d_{Ir\text{-}C1}$ (Å)	$d_{Cp^*\text{-}Ir}$ (Å)	$d_{Ir\text{-}N}$ (Å)	$\theta_{C1\text{-}Ir\text{-}N}$ (°)
Ir3c	2.035	1.839	2.096	77.43
Ir3e	2.032	1.825	2.074	76.65
Ir3f	2.048	1.837	2.079	76.87
Ir4a	2.021	1.824	2.095	77.67
Ir4b	2.048	1.812	2.100	78.13
Ir4d	2.041	1.811	2.090	78.11

Figure 1. ORTEP representations of selected iridium complexes and key parameters (d = distance, θ = angle). Thermal ellipsoids are at 50% probability and hydrogen atoms are omitted for clarity.[23]

Substrate scope of the reductions and functional group compatibility

We next evaluated the generality of the reduction process. Using the optimized reaction conditions and catalyst **Ir4a**, a large array of oximes **1** were reduced to the corresponding *N*-hydroxy or *N*-alkoxyamines **2** in excellent yields (Scheme 4). Noteworthy, the *E*/*Z*-stereochemistry of the substrate is inconsequential for the reaction performance.[19,10a] We first evaluated *N*-alkoxy derivatives of relevant α-alkyl benzylamines (R^1 = Ar, R^2 = alkyl).[20a-c] Regarding the oxime *O*-substitution pattern, different bulk defined as 1°, 2° or 3° alkyl ethers (**1b-1e**) reacted smoothly and were reduced in virtually quantitative yields. Remarkably, unsubstituted oximes reacted equally well and gave corresponding hydroxylamines (**2f**, **2pc**) without any detectable N-O bond cleavage. Benzyl ethers (**2c**, **2pd**) proved to be stable towards hydrogenolytic cleavage of the benzyl group. Products having different *p*-substituted aryl units, such as **2b** (*p*-OMe), **2ga** (*p*-Me), and **2gb** (*p*-F), were accessed in excellent yields. The *o*-CH_3Ph analogue **1gc** reacted more sluggishly due to steric hindrance close to the reaction site. A similar behaviour was observed for products **2i** and **2j** bearing bulkier 2° alkyl substituents. In these cases, simply replacing *i*PrOH by MeOH as solvent increased the yields. The use of triflic acid was found to be beneficial for less basic oxime **1ib**. Noteworthy, the nitro group of **2j** remained fully intact and was not reduced, showcasing the unique chemo-selectivity of this hydrogenation protocol. Heterocyclic benzoxazine scaffolds **2ka** and **2kb** were accessed in quantitative yield. Ferrocene- and benzothiophene-containing products **2h** and **2l** were obtained in excellent yield. The latter is the immediate precursor for the synthesis of the marketed anti-asthma drug Zileuton.[20c] Additionally, hydrogenation of biologically active Fluvoxamine[20d] (protected as its *N'*-phthalimido derivative) afforded reduced variant **2m**. We next targeted substrates with additional substitutions (R^1 and R^2) at the oxime Csp^2 atom. For instance, a linear *N*-benzylamine product **2n** (R^2 = H) was formed by reduction of its aldoxime precursor. Moreover, a diaryl ketoxime (R^1, R^2 = aryl) was also hydrogenated to corresponding α,α-diarylamine **2o**, albeit in reduced yield. Several oximes having aliphatic substituents R^1 and R^2 were smoothly hydrogenated to give medium and small cycloalkane-containing *N*-alkoxy amines **2pa-2pe**. Bulkier α-alkyl oximes **1q** and **1r** were reduced as well. The method is suitable to access *N*-alkoxy derivatives of amphetamine **2s**[20e] as well as 1,2-amino alcohols **2a**.

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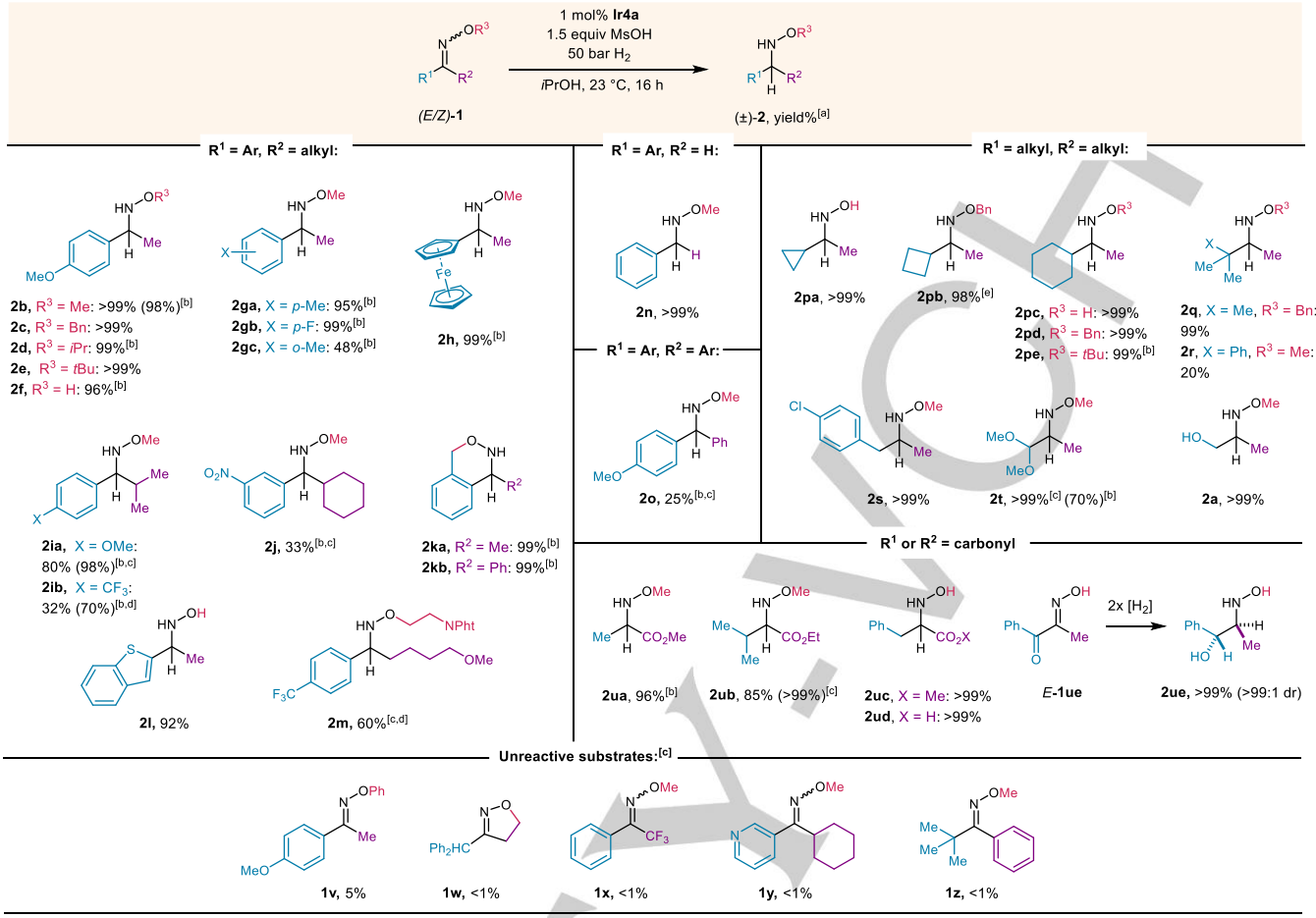

Scheme 4. Substrate scope of the hydrogenation process. Reaction conditions: 0.30 mmol **1**, 0.45 mmol MsOH, 3 µmol **Ir4a** in *i*PrOH (0.3 mL) at 23 °C for 16 h. [a] Yields determined by ^{1}H-NMR using 1,3,5-trimethoxybenzene as internal standard; in all entries the yield equals the conversion of the oxime starting material. [b] isolated yield. [c] in MeOH. [d] with triflic acid. [e] The crude product was *N*-benzoylated prior to isolation.

Notably, the dimethoxy acetal moiety of **2t** remained intact during the acidic reduction conditions. The use of anhydrous methanol was needed to prevent hydrolysis. Oximes with adjacent carboxylic acids or esters ($R^2 = CO_2X$) were suitable substrates and smoothly hydrogenated in excellent yields. This enables a convenient access to relevant *N*-hydroxy or *N*-alkoxy derivatives of α-amino acids (**2ua-2ud**).[20f,g] Finally, *N*-hydroxyl norephedrine **2ue**[20e] was obtained quantitatively from **1ue**. Notably the double reduction of α-keto oxime precursor **1ue** proceeded in a highly diastereoselective fashion and only a single diastereoisomer was observed. Surprisingly few substrates were refractory to the standard hydrogenation conditions. For instance, O-phenyl substitution of **1v** might provide extra stabilization to the oxime C=N double bond by conjugation hampering reaction. 4,5-Dihydroisoxazole **1w** was not reduced, presumably due to high steric congestion at the reactive site. Counterintuitively, a CF_3 substituent in **1x** which enhances the electrophilicity of the Csp^2 center towards hydride attack, was detrimental. In this case, the further reduced basicity of the oxime impedes its activation by *N*-protonation. A similar effect may be responsible for pyridyl-bearing oxime **1y**, which did not react even in the presence of an extra equivalent of acid to blunt the coordinating ability of the pyridine ring. The pairing of *t*Bu/Ph substitution (**1z**) proved to be beyond the tolerance limit of catalyst **Ir4a**. Comparatively, a sterically leaner chiral catalyst[10a] was able to reduce **1z** in 90% yield under otherwise identical reaction conditions.

Subsequently, the functional group tolerability was further checked by selected additive tests using the reduction of oxime **1b** using catalyst **Ir4a** (Scheme 5).[10a, 21] With the substrate scope studies, these provide the full picture of the exquisite functional group compatibility displayed by this acidic hydrogenation protocol. The best scenario for which additive **5** is fully recovered and **1b** is quantitatively converted to **2b** was observed for a host of functional groups. These include aniline **5a**, benzofuran **5b**, styrene **5c**, *N,N*-dimethylbenzamide **5d**, phosphine oxide **5e**, and phenyl boronic ester **5f**. The addition of a ketone (**5g**), imine (**5h**) or quinoline (**5i**) did not interfere with the reduction, allowing the quantitative formation of **2b**. However, these additives were reduced to their respective alcohol, amine and tetrahydroquinoline products **6g**-**6i**. Pyridine (**5j**) or benzonitrile additives (**5k**) remained intact but slow down the reduction of **1b**. This can be attributed to their coordinating properties to the iridium center through their basic nitrogen atom. Similarly, halide impurities poison the catalyst (*vide infra*). This might explain the partial reduction of **1b** in the presence of *unpurified* iodobenzene **5l**. Lewis basic Ph_3P (**5n**) and sulfoxide **5o** remain stable but suppress catalysis. Internal alkyne **5m** disappears to a complex mixture of products and prevents oxime reduction.

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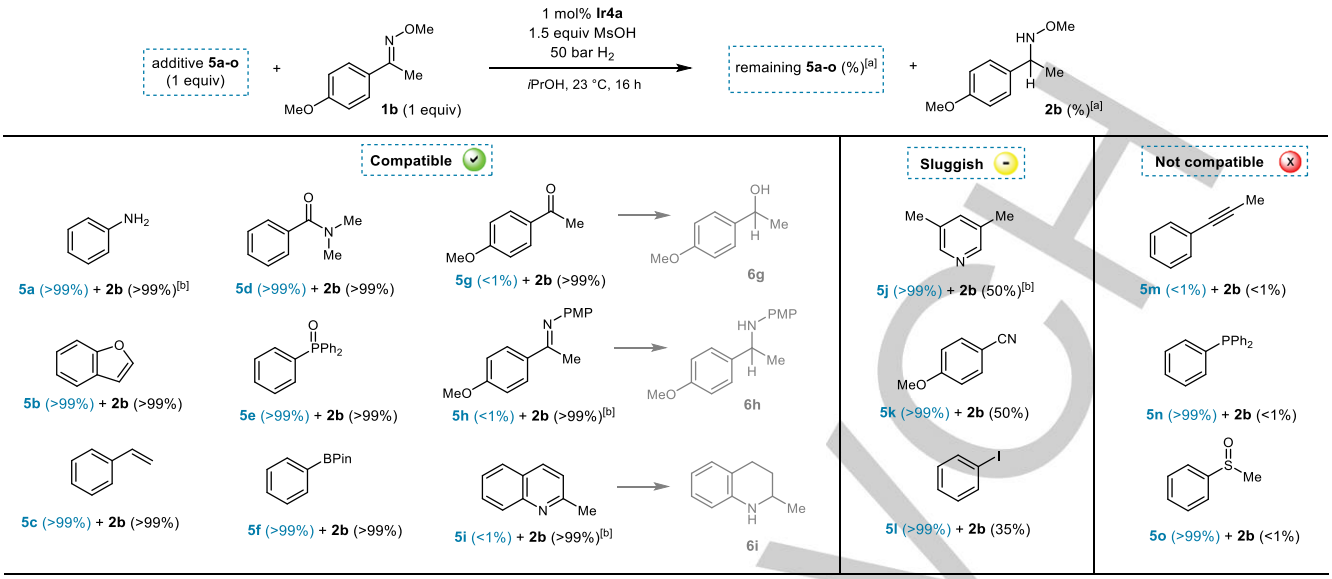
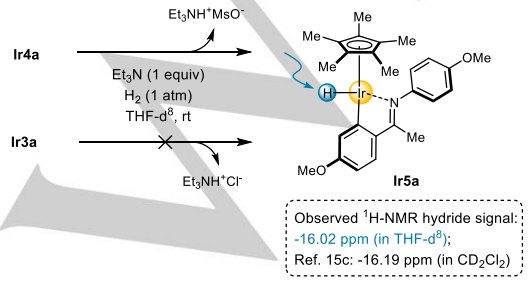


Scheme 5. Further functional group compatibility of the oxime hydrogenation by additive tests. Reaction conditions: 0.1 mmol *E*-**1b**, 1 equiv. additive **5**, 1 mol% **Ir4a**, 50 bar H_2, 1.5 equiv. MsOH, 0.5 M in *i*PrOH, 23 °C, 20 h. [a]Yield determined by ^{1}H-NMR using 1,3,5-trimethoxybenzene as the internal standard; for all cases the yield of **2b** is virtually identical to the consumption of **1b**; [b]with 2.5 equiv. MsOH

Mechanistic insight of the reduction

Having developed Cp*Ir(III) complexes that are highly efficient catalysts for selective oxime hydrogenations in the presence of a strong acid, several parts of their mode of operation remained uncertain. This knowledge might be of help in the design of improved second-generation catalysts. In principle, catalytic hydrogenations can be formally dissected into two core mechanistic events: the hydride formation by dihydrogen activation and the subsequent hydride transfer.[3a, 22h] In this respect, we attempted the stoichiometric formation of the active iridium hydride species **Ir5a** (Scheme 6). Xiao *et al.* described a synthesis from chloride **Ir3a** with the hydride originating from triethylammonium formate.[15c] Subsequent isolation and X-Ray analysis provided solid evidence of its identity, and ^{1}H-NMR analysis in CD_2Cl_2 revealed a hydride peak at -16.19 ppm. In a NMR tube, we observed complete conversion of methanesulfonate complex **Ir4a** to **Ir5a** after 16 h with one atmosphere of hydrogen gas using d^8-THF as the solvent. The characteristic hydride peak at -16.02 ppm was detected. Equimolar amounts of triethylamine were needed to quench the MsOH byproduct driving the reaction to completion (see SI for full details). In contrast, chloride bearing complex **Ir3a** was not competent to form **Ir5a** under the same reaction conditions.



Scheme 6. Stoichiometric iridium hydride formation.

We thus hypothesized that a weakly coordinating anion, such as methanesulfonate, was essential to spontaneously dissociate from 18-electron iridium complex **Ir4a**, allowing dihydrogen coordination and subsequent formation of the active hydride species **Ir5a**. We validated this hypothesis in the catalytic hydrogenation of **1b** (Table 2, entries 1-4). Negligible catalytic activity was observed for chloride complex **Ir3a** (entry 1). In contrast, using **Ir4a** and **Ir6a** bearing weakly basic O-binding methanesulfonate or trifluoroacetate counter ions, led to quantitative formation of product **2b** (entries 2-3). Likewise, excellent reactivity was observed with the cationic complex **Ir7a**, featuring a non-coordinating tetrafluoroborate counteranion (entry 4). The results imply that any chloride impurities present in the reaction media have the capability to poison the catalyst.[3a] To maximize catalyst efficiencies, brine-wash work-up procedures without additional substrate purification steps should be avoided, and low chloride source of MsOH should be preferred. The hydrogen pressure is a relevant factor (entries 2, 5-7). Oxime **1b** is completely reduced after 3 h at 10 bar of hydrogen gas (using 1 mol% **Ir4a**). Almost no difference is found with higher pressures. Under identical conditions, using just a balloon of hydrogen reduced the reactivity and gave 66% yield in the same time frame (entry 6). This outlines the feasibility of conducting oxime hydrogenations at convenient atmospheric pressure if the maximum catalytic efficiency is not a top priority. From the mechanistic standpoint, H_2 is likely to become involved in the rate-determining step (RDS) of the hydrogenation somewhere below 10 bar. At higher pressures, the hydride transfer presumably becomes the RDS. A control experiment showed the formation of just traces amounts of **2b** in the absence of H_2 gas (entry 7), indicating a very weak background reactivity *via* hydrogen transfer from *i*PrOH.[22a]

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Table 2. Influence of anionic ligand (X) and hydrogen pressure on the oxime reduction.[a]

Entry	[Ir]	X	H_2 pressure	Yield (%)[b]
1	**3a**	Cl^-	50 bar	<5
2	**4a**	MsO^-	50 bar	>99
3	**6a**	TFA^-	50 bar	99
4	**7a**	BF_4^- [c]	50 bar	95
5[d]	**4a**	MsO^-	10 bar	>99
6[d]	**4a**	MsO^-	1 bar	66
7[d]	**4a**	MsO^-	no H_2	3

[a] Conditions: 0.30 mmol **1b**, 0.45 mmol MsOH, 0.75 µmol [**Ir**] in solvent (2 mL) at 23 °C for 3 h; [b] yield determined by ^{1}H-NMR using 1,3,5-trimethoxybenzene as internal standard, being equal to the conversion of the oxime starting material unless otherwise stated; [c] as its mono acetonitrile adduct, crystal structure included in the SI;[23] [d] With 1 mol% **Ir**.

We next investigated the effect of different amounts of the Brønsted acid on the reaction rate (Figure 2). For instance, a run with 0.25 mol% **Ir4a** and an excess of acid (1.5 equivalents MsOH with respect to **1b)**, reached full conversion to product **2b** within 30 minutes. A further increase of the acid concentration to 3.0 equivalents did not results in any increase of the reaction rate. In contrast, reducing the amount of MsOH to 0.75 equivalents caused a stall of the conversion of **1b** at 70%. This observation is fully consistent with a mandatory protonation of the oxime for reaction. In case of substoichiometric amounts of acid, the more basic alkoxy amine product scavenges all available protons forming stable ammonium salts. The slightly slower *initial* reaction rate (data point at 5 minute reaction time) might suggest that the role of the Brønsted acid extends beyond oxime protonation, as this process should be fast and near-quantitative with methanesulfonic acid having a pKa of -1.9.[12d] For instance, it has been proposed that the conjugated base may assist the heterolytic cleavage of H_2 into a hydride and a proton.[22b,c] Separate studies of the impact of the acid strength on reactivity revealed that TFA (pKa = 0.23)[12d] as the weakest acid still allowing the process.[10a] Noteworthy, we have not found in any case an induction period, indicating that dissociation of the methanesulfonate ligand from the initial catalyst species is not the RDS.

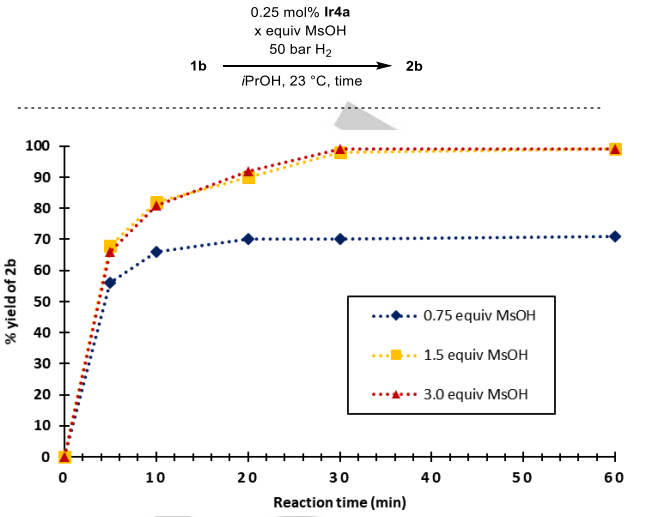

Figure 2. Influence of the acid concentration in the reaction rate. Conditions: 0.3 mmol **1a**, 0.23 / 0.45 / 0.90 mmol MsOH, 0.25 mol% **Ir4a,** 50 bar H_2 in *i*PrOH (0.3 mL) at 23 °C; yield of **2b** determined by ^{1}H-NMR using 1,3,5-trimethoxybenzene as internal standard, being equal to the conversion of **1b**.

Considering all aspects, the following hydrogenation mechanism can be suggested (Scheme 7). Initial dissociation of the methanesulfonate counter ion from coordinatively saturated complex **[Ir-OMs]** (likely favored in polar solvents) forms 16-electron cationic complex **[Ir]$^+$**. Dihydrogen η^2-coordination to iridium generates **[IrH$_2$]$^+$** complex. This species has been calculated to be super-acidic,[22d] even more acidic than MsOH, thus favoring heterolytic splitting of H_2 into iridium hydride species **[Ir-H]** and MsOH. The conjugated base, in this case mesylate, and protic solvents have been demonstrated to accelerate this step.[22e] Separately, oxime substrate **1** is activated by protonation with MsOH forming **1-H$^+$** with enhanced electrophilicity. Next, the uncoordinated **1-H$^+$** is reduced by separately receiving a hydride from **[Ir-H]** and subsequently a proton from MsOH. This outer-sphere hydrogenation mechanism is termed ionic hydrogenation.[22f-i] It has as well been proposed for related catalytic imine hydrogenations.[14d, 22j, 22k] In the present case, the hydride transfer from **[Ir-H]** to **1-H$^+$** seems to be the rate-limiting step of the catalytic cycle. Rapid *N*-protonation of alkoxy amine product as the most basic entity in the reaction mixture occurs rapidly by MsOH forming salt **2-H$^+$**. Outside the cycle, free base **2** is obtained upon basic work-up.

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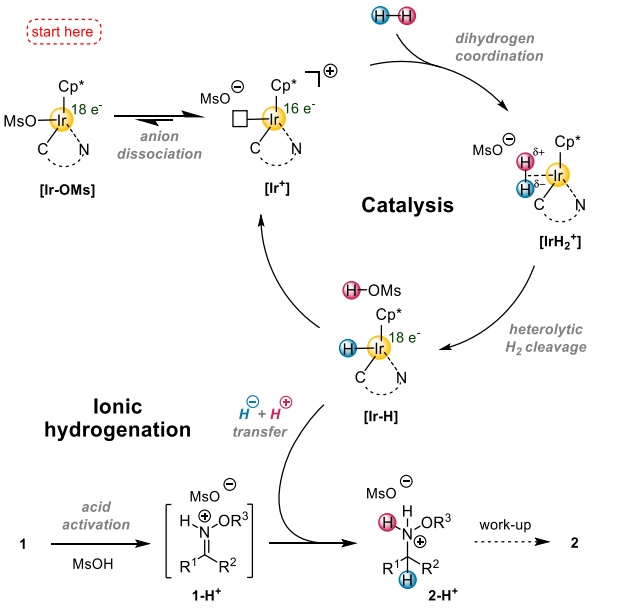

Scheme 7. Suggested reaction mechanism of the ionic iridium-catalyzed oxime hydrogenation.

Conclusion

We report a class of cyclometalated cyclopentadienyl iridium(III) complexes. These iridacycles are air and moisture stable and are synthesized in a simple and straight-forward manner. In conjunction with strong acids, these complexes are highly active catalysts for the homogeneous hydrogenation of oximes and oxime ethers to hydroxylamines and alkoxyamines. Structural activity relationship studies of different iridium complex analogs revealed some features of the ligand design, setting the basis for improved catalytic activity. The oxime substrate scope for the hydrogenation is very broad and occurs without any detectable cleavage of the weak N-O bond, which is considered a persistent and undesired side-reaction. Remarkably, the reduction process proceeds at room temperature and is operationally simple. Experimental evidence indicates that an ionic hydrogenation mechanism is operative, with the hydride transfer from the iridium hydride species to the substrate being the rate limiting step of the catalytic cycle. We believe that the described mechanistic understanding will further foster implementation of the metal-catalyzed acid-assisted ionic hydrogenations for the reduction of other challenging substrate classes and functional groups.

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Keywords: Homogeneous catalysis • Hydrogenation • Iridium • Oxime • Hydroxylamine

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[23] Deposition Numbers 2064725 (**Ir4a**), 2064726 (**Ir7a**), 2064727 (**Ir3e**), 2064728 (**Ir3f**), 2064729 (**Ir4d**), 2064730 (**Ir3c**), and 2064731 (**Ir4b**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures.

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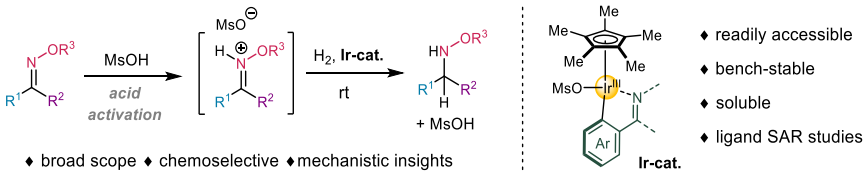

Half sandwich iridium(III) complexes are found to be efficient catalysts for homogeneous oxime hydrogenation to hydroxylamine products. Only if equipped with an aryl imine ligand and operating under strong acidic conditions. Remarkably they do not hydrogenolyse the fragile N-O bond. Experimental evidence suggests an unusual acid-assisted ionic hydrogenation mechanism which may be applicable to the reduction of other challenging substrates.