How to cite: *Angew. Chem. Int. Ed.* **2024**, *63*, e202404955
doi.org/10.1002/anie.202404955

Asymmetric Hydrogenation

Cyclometallated Imides as Templates for the H-Bond Directed Iridium-Catalyzed Asymmetric Hydrogenation of *N*-Methyl, *N*-Alkyl and *N*-Aryl Imines

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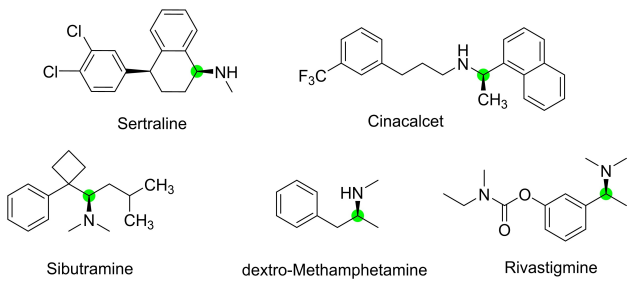
Abstract: A combined computational and experimental approach allowed us to develop overall the most selective catalyst for the direct hydrogenation of *N*-methyl, *N*-alkyl and *N*-aryl imines described to date. Iridium catalysts with a cyclometallated cyclic imide group provide selectivity of up to 99 % enantiomeric excess. Computational studies show that the selectivity results from the combined effect of H-bonding of the imide C=O with the substrate iminium ion and a stabilizing π–π interaction with the cyclometallated ligand. The cyclometallated ligand thus exhibits a unique mode of action, serving as a template for the H-bond directed approach of the substrate which results in enhanced selectivity. The catalyst (**2**) has been synthesized and isolated as a crystalline air-stable solid. X-ray analysis of **2** confirmed the structure of the catalyst and the correct position of the imide C=O groups to engage in an H-bond with the substrate. ^{19}F NMR real-time monitoring showed the hydrogenation of *N*-methyl imines catalyzed by **2** is very fast, with a TOF of approx. 3500 h^{-1}.

Introduction

Chiral amines are key building blocks in many natural bioactive compounds and pharmaceuticals.[1] Although biocatalytic and organocatalytic strategies have gained importance in the synthesis of chiral amines, the metal-catalyzed asymmetric hydrogenation (AH) of imines and enamides remains a significant pathway to this class of compounds.[2] The AH of imines offers excellent atom economy and it is a sustainable approach to prepare optically active amines. The industrial synthesis of (*S*)-metolachlor nicely exemplifies these principles.[3] In this arena, most research efforts have been devoted to the hydrogenation of *N*-aryl imines.[4] In comparison, little attention has been given to the AH of *N*-methyl and *N*-alkyl imines (Scheme 1).[5] This is because the product *N*-alkyl amines are more basic and thus tend to cause catalyst deactivation. Such deactivation can be circumvented by hydrosilylation or organocatalytic reduction in the presence of Boc_2O.[6] However, a subsequent deprotection step is necessary in these cases and therefore direct AH is a much more advantageous process.

In this field, we reported the first catalyst active in the direct AH of *N*-methyl and *N*-alkyl imines.[7] The catalyst was an iridium (III) complex containing a P-stereogenic MaxPHOX P,N-ligand and a cyclometallated *N*-phenyl imine which afforded selectivities in the 89–94 % ee range. While H-bond-assisted substrate pre-organization has been used in organocatalytic and metal-catalyzed processes, to



Scheme 1. Chiral *N*-methyl and *N*-alky amine fragments contained in several drugs.

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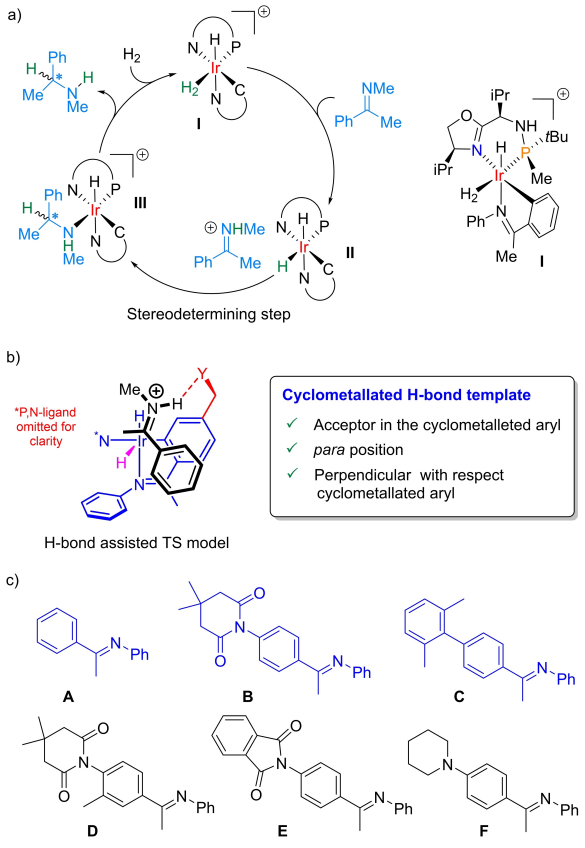
our knowledge, this strategy has never been exploited in the metal-catalyzed asymmetric hydrogenation of imines.[8] Here, we report a family of iridium catalysts containing an H-bond acceptor group which provide an unprecedented mechanism of action for the reduction of imines. The new catalysts provide enhanced selectivity (up to 99% ee) and activity (up to 3500 h^{-1} TOF) for the challenging *N*-methyl and *N*-alkyl imine substrates.

Results and Discussion

In a groundbreaking study some years ago, Pfaltz and co-workers revealed that the catalyst in the iridium-P,N-catalyzed AH of *N*-aryl imines contains a cyclometallated imine substrate.[9] Computational studies of this process confirmed that it follows an outer-sphere mechanism like the one shown in Scheme 2a.[10] The catalyst is a cationic octahedral Ir(III) complex with hydride and dihydrogen ligands (**I**). The acidity of **I** protonates the imine, thereby activating the substrate. The critical stereodetermining step is the hydride transfer from the neutral iridium dihydride **II** to the iminium ion. This elementary step has a very loose transition state (TS) in which multiple orientations of the iminium ion are possible and where subtle non-covalent interactions between the cyclometallated imine and the substrate determine the stereochemical outcome of the reaction.



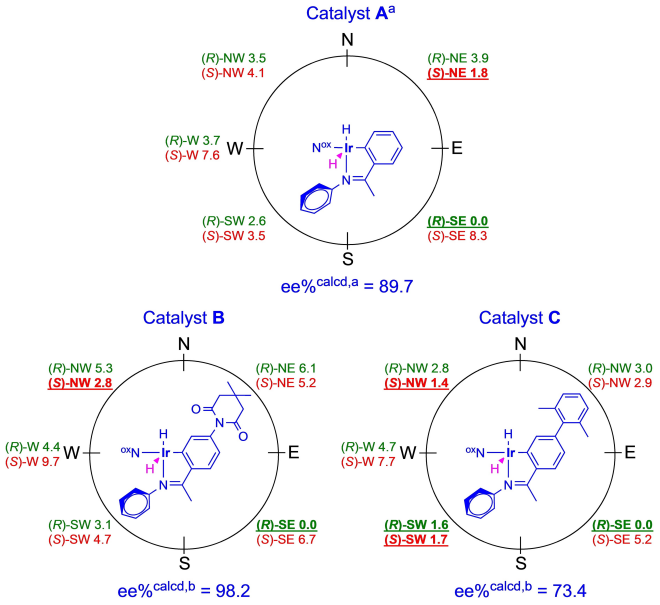
Scheme 2. a) Imine hydrogenation mechanism with Ir–P,N catalysts. b) Model transition state and H-bond acceptor. c) Cyclometallating agents used in the computational model (blue) and in the experimental study.

In particular, the computational analysis unveiled the NH cation-π interaction, in addition to the large π–π interaction between the substrate and cyclometallated aromatic groups, as the key recognition factors in the TS.[7] Inspired by these insights, we reasoned that a properly placed H-bond acceptor group could engage in an attractive interaction with the iminium moiety and work as an H-bond template for the guided approach of the substrate, potentially enhancing the selectivity of the process (Scheme 2b). We hypothesized that, for an effective H-bond to occur, the acceptor group should be placed at the *para* position and it should stand perpendicular above the cyclometallated arene, as depicted in Scheme 2b. We thought that a cyclic imide group attached at the *para* position of the cyclometallating imine fulfilled all these requirements. We postulated that the imide ring would be perpendicular to the attached arene, thus positioning the acceptor C=O group in the direction of the iminium ion. With this in mind, we undertook a computational study using imine **B**, which contains an imide group at the *para* position of the C=N function. For comparison purposes, we also modelled **C**, in which no H-bond acceptor groups are located at the imide moiety, and we compared them all with the standard imine **A** (Scheme 2c).

The stereodetermining hydride transfer was modelled at B3LYP-D3 level in DCM continuum solvent for activated iridium dihydride catalysts **B** and **C** (see Supporting Information for full details). In analogy to our previous DFT analysis over the original catalyst **A**, a series of multiple orientations of the iminium ion contribute to the stereochemical outcome of the reaction. Five different TSs, differing in the orientation of the substrate with respect to the catalyst were characterized for the generation of the two enantiomers. Considering the relative population of the five TS, computed ee% of 98.2 and 73.4 were obtained for catalyst **B** and **C**, respectively. The results, together with the previous computed ee% for catalysts **A**, are shown in Scheme 3.

Figure 1 shows the comparison between the Non-Covalent Interactions (NCIs) for the two lowest TSs computed for catalyst **B**, leading to the formation of the *R* and *S* products, pro-R^{SE} and pro-S^{NW}, respectively. The NCI analysis does predict the H-bond between the C=O group of the imide and the iminium ion. However, this interaction is observed for both pro-R^{SE} and pro-S^{NW} orientations. The energy gain of 2.8 kcal·mol^{-1} computed for the pro-R^{SE} TS leading to the major product compared to the pro-S^{NW} is due to the large π–π interaction between the substrate and cyclometallated aromatic groups. Instead of this interaction, the lowest pro-S^{NW} TS presents a weaker CH-π interaction in this region.

It is important to note that the directing group stabilizes those conformations able to establish a H-bond, i.e. pro-R^{SE} and pro-S^{NW}, making the other TSs non-competitive. Moreover, the bulky cyclic imide group hinders the pro-S^{NE} orientation, which is favored in the original catalyst **A** (see Scheme 1), contributing to an increased ee. On the other



Scheme 3. DFT computed quadrant model for the hydrogenation of acetophenone *N*-methyl imine with catalyst containing cyclometallated imine A,, B and C . Transition state relative $\Delta\Delta G_{DCM}^{\ddagger}$ values for different orientations of the substrate phenyl group (in green: TSs leading to *R* isomer; in red: TSs leading to *S* isomer). The hydride transferred to the substrate is highlighted in magenta. The competitive TSs are highlighted in bold and underlined. Computed ee% over the complete set of TSs are reported for catalysts **A**, **B** and **C** (bottom). [a] Values adapted from [7] for the R enantiomeric series. [b] This work, values computed at B3LYP-D3/def2-TZVP, def2-QZVP(Ir)/SMD(DCM)// B3LYP-D3/6-31G(d,p), SDD + f(Ir)/SMD(DCM) considering the complete set of 5 pro-*S* and five pro-*R* TSs.

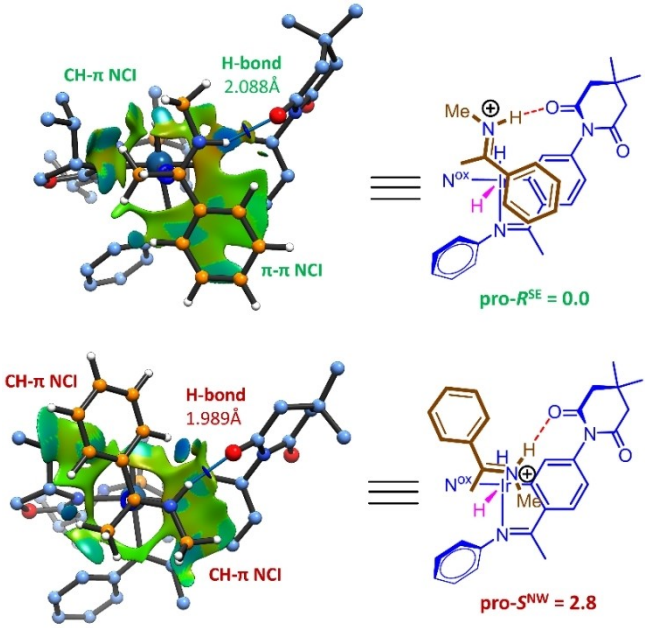


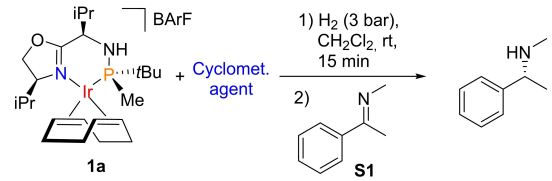
Figure 1. Comparison of the NCIs for the two lowest transition states for the hydrogenation of acetophenone *N*-methyl imine with catalyst **B**. NCIs are represented as blue (strong), green (weak) and red (repulsive) surfaces. $\Delta\Delta G_{DCM}^{\ddagger}$ values are given in kcal·mol^{-1}.

hand, for the control catalyst **C**, the absence of directing groups, make other pro-*S* orientations, i.e. pro-S^{NW} and pro-S^{SW}, competitive, lowering the computed ee% from 98.1 down to 73.4 (see Scheme 3).

With this data in hand, to confirm the hypothesis experimentally, we proceeded to synthesize imide **B** and two additional cyclometallating agents, namely **D** and **E**, which also contain an imide *para* to the C=N function, and the control compounds **A**, **C** and **F** (Scheme 2c). Compounds **A-F** were compared in the AH of acetophenone *N*-methyl imine as a test substrate (Table 1). The catalysts (1 mol%) were pre-formed in situ by mixing [Ir(MaxPHOX)(cod)] BArF with 2 equiv. of cyclometallating agent at 3 bar of H_2 in DCM. The substrate was then added via a syringe and the reaction was stirred at room temperature overnight. Addition of the standard cyclometallating agent **A** afforded the product amine with 90% ee (Table 1, entry 2). In contrast, cyclometallating agents **B**, **D** and **E** containing H-bond acceptor imide groups provided significantly higher ees (Table 1, entries 3–5). Compound **D**, with a methyl group in ortho position with respect to the glutarimide, provided the highest selectivity (97% ee) (Table 1, entry 5). The reaction was also evaluated with compound **C** and **F** which contain a 2,6-dimethylbenzene and a piperidine group respectively (Table 1, entries 6 and 7). In this case, the selectivity dropped to 69 and 89% ee. The difference in selectivity between **B**, **D**, **E** and **C, F** supports the notion that the enhancement in selectivity is not due solely to steric effects but to the H-bonding with the imide that directs and limits the number of competitive orientations of the substrate.[11]

Next, we addressed the hydrogenation scope of the new catalytic system generated in situ with several *N*-methyl and *N*-alkyl imines using cyclometallating agent **D** (Figure 2). Full conversions were attained in all cases employing 1 mol% catalyst loading, as determined by ^{1}H NMR analysis. In some instances, reactions were carried out at reduced temperature (0 or −10 °C) to optimize selectivity. In general,

Table 1: Performance of the cyclometallating agents.[a]



Entry	Cyclometallating agent	Temp. (°C)	Conv. (%)	ee (%)
1	none	rt	100	13[a]
2	**A**	rt	100	90[a]
3	**B**	rt	100	96
4	**E**	rt	100	96
5	**D**	rt	100	97
6	**C**	rt	100	69
7	**F**	rt	100	89

[a] Cyclometallated catalyst pre-formed in situ with 1 mol% [Ir(MaxPHOX)(cod)] BArF, 2 mol% cyclometallating agent in DCM at room temperature and 3 bar of H_2 for 15 min. [b] Previous results, see ref. [7].

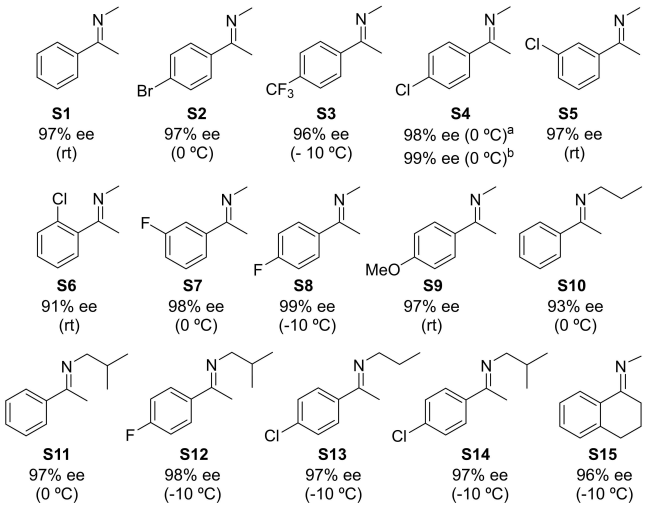
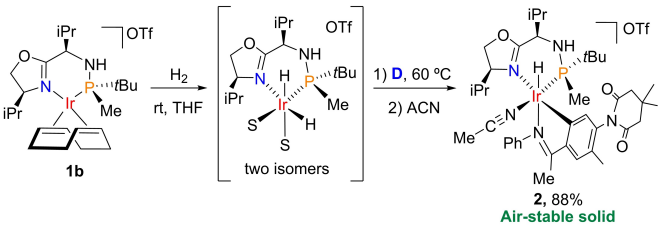


Figure 2. Results for the hydrogenation of *N*-methyl and *N*-alkyl imines using cyclometallating agent **D**. The catalyst was pre-formed in situ. Hydrogenation reactions were run overnight in DCM at 3 bar of H_2 with 1 mol% of catalyst at the temperature listed. 100% conversion was obtained in all cases, as determined by ^{1}H NMR . Enantiomeric excess was determined by chiral HPLC or GC of the corresponding trifluoroacetamide. a) Gram-scale reaction. b) Using cyclometallating agent **E**.

between 96 and 97 % ee was obtained for most substrates, including several *N*-propyl (**S10** and **S13**) and *N*-isobutyl imines (**S11**, **S12** and **S14**). Substitution in ortho position appeared to produce a slight decrease in selectivity since the reduction of *o*-chloro *N*-methyl imine **S6** afforded 91 % ee. Hydrogenation of the bicyclic *N*-methyl imine of 2-tetralone **S15** also occurred in high selectivity (96 % ee). In certain cases, the use of additive **E** led to a slight increase in selectivity (Figure 2, S4). Most remarkably, an unprecedented 99 % ee was attained for **S4** and **S8** *N*-methyl imines.

Next, we focused our efforts on the isolation of the catalytic cyclometallated species. Initial attempts to prepare the cyclometallated catalyst were conducted using similar conditions employed for the in situ preparation of the catalysts. However, mixing [Ir(MaxPHOX)(cod)] BArF with additive **D** under hydrogen at room temperature provided oily mixtures, from which the cyclometallated compound could be neither purified nor crystallized. After some experimentation, we found that switching the counterion from BArF to TfO produced solid mixtures with variable amounts (50–80 %) of the desired Ir(III) hydride. Finally, we determined that the best way to conduct the cyclometallation was through thermal activation. The optimized two-step one-pot synthesis of cyclometallated **2** is depicted in Scheme 4. In this regard, [Ir(MaxPHOX)(cod)] TfO (**1**) was hydrogenated at low pressure in THF to remove the 1,5-cyclooctadiene (cod) ligand. The resulting intermediate is a mixture of two iridium (III) dihydride isomers with two THF molecules coordinated to the metal.[12] Hydrogen was then removed, an excess of imine additive **D** was added, and the mixture was heated for 12 h under nitrogen. Upon completion of the reaction, acetonitrile was added to stabilize the resulting vacant



Scheme 4. Synthesis of cyclometallated catalyst **2**.

coordination position. After chromatographic purification using DCM/ACN solvent mixtures, cyclometallated **2** was isolated in 88 % yield as a pale-yellow air-stable crystalline solid.

To confirm the structure of **2**, single crystals were grown by layering DCM and heptane. The resulting X-ray solid-state structure of **2** is shown in Figure 3.[13] The iridium displays an octahedral coordination. The oxazoline nitrogen atom is *trans* with respect the cyclometallated aryl, while the imine nitrogen is *trans* to the hydride ligand. The X-ray structure confirmed that the putative reaction site is occupied by an acetonitrile molecule *trans* to phosphorus. Also, as predicted, the cyclic imide is perpendicular to the cyclometallated arene, and thus the H-bond acceptor C=O group is pointed at the reaction center. Finally, correlation NOESY experiments confirmed that this same structure is also present in solution (see Supporting Information).

After isolation and characterization of **2**, we proceeded to test it in the hydrogenation of imines (Figure 4). Most gratifyingly, **2** showed parallel activity and selectivity with respect to the catalysts generated in situ for the reduction of *N*-methyl imines. Catalyst **2** was also tested in the hydrogenation of *N*-benzyl (**S17**) and *N*-aryl imines (**S18–23**) with selectivities in the 97–98 % ee range for this type of substrates. Catalyst **2** demonstrated to be effective and viable in a gram-scale hydrogenation, providing, in this case, the corresponding 4-chlorophenyl substituted amine with 98 % ee (Figure 4b). Finally, the enantiomeric form of **2** was employed in a formal synthesis of Rivastigmine (Figure 4c). 3-Methyoxyacetophenone (**S24**) *N*-methyl imine was reduced to the corresponding amine in 95 % yield and 95 % ee

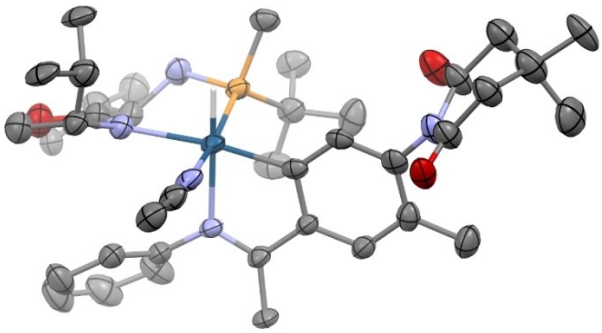


Figure 3. X-ray structure of **2**. The Ortep diagram shows ellipsoids at 50% probability. Only the H attached to iridium is drawn. TfO counterion and a co-crystallized DCM solvent molecule are omitted for clarity.

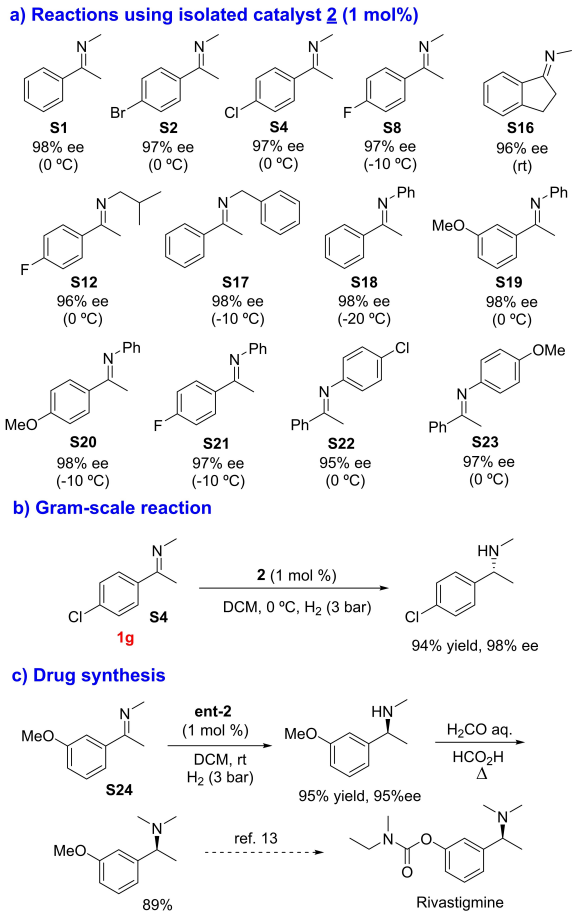


Figure 4. Assessment of isolated catalyst **2** in the asymmetric hydrogenation of different imines. Conversions are 100% as determined by ^{1}H NMR.

and then alkylated to the corresponding dimethylamine. Demethylation of the methoxy group and carbamate formation leads to Rivastigmine in a short and selective synthesis.[14] These results indicate the generality of the H-bonding template strategy for other classes of imine substrates. Also, they demonstrate that the large BArF counterion is not necessary for efficient catalysis and that the acetonitrile solvent molecule can work efficiently as transient ligand for the catalytic active site.

To assess the activity of catalyst **2**, we monitored the hydrogenation of 4'-(trifluoromethyl)acetophenone *N*-methyl imine (**S3**) by ^{19}F NMR on a 1.4T bench-top spectrometer (Figure 5). Monitoring was performed by bubbling H_2 at 3 bar of pressure in the NMR tube. The concentration of catalyst was set constant at 0.2 mM and the probe temperature was 37 °C (see Supporting Information for details on hydrogenation setup). Under these conditions, at 10–50 mM of imine, the hydrogenation was extremely fast and TOF remained approximately constant, at around 3500 h^{-1}.[15] Reaction at 0.4 mol% (50 mM) reached full conversion in 4.3 min (yellow trace). However, increasing the concentration of imine starting material to 100 mM (blue trace) resulted in hydrogenation stalling at around 40% conversion. In a catalyst stability test, **2** was incubated with 10

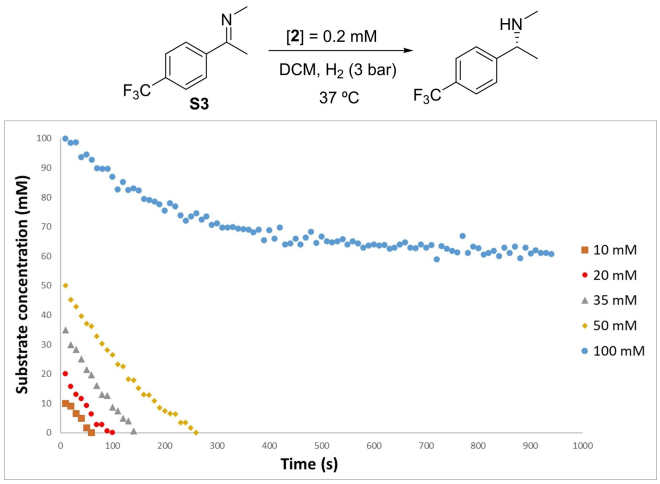
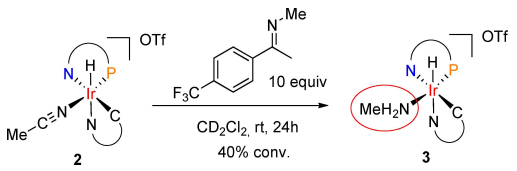


Figure 5. Kinetic profile of the hydrogenation of 4'-(trifluoromethyl) acetophenone *N*-methyl imine by ^{19}F NMR . Disappearance of starting imine plotted against time. The temperature of the NMR probe was constant at 37 °C. [**2**] = 0.2 mM for all experiments. [imine] = 10, 20, 35, 50 and 100 mM.

equiv. of starting imine (**S3**) at room temperature in the absence of hydrogen (Scheme 5). After 24 h, the initial Ir-acetonitrile complex was partially transformed into the corresponding Ir-methylamine complex **3**, as determined by mass spectrometry and independent synthesis. Moreover, when complex **3** was synthesized independently, it showed to be completely inactive in catalysis. These facts, strongly suggest that methylamine resulting from imine hydrolysis produces the inactivation of the catalyst and is responsible for reaction termination at higher concentration of substrate.[16]

Conclusion

In summary, a combined computational and experimental approach allowed us to develop the most selective catalysts for the direct hydrogenation of *N*-methyl and *N*-alkyl imines described to date. These are iridium (III) catalysts containing a P,N-MaxPHOX ligand and a cyclometallated imine with a cyclic imide group. Upon generation of the catalysts in situ, selectivities from 91 to 99% ee were achieved with several *N*-methyl, *N*-alkyl and *N*-aryl imines. NCI analysis confirmed that the high selectivity results from the combined effect of the H-bond with the substrate iminium ion and a stabilizing π–π interaction with the cyclometallated



Scheme 5. In a stability test catalyst **2** was incubated in CD_2Cl_2 solution with 10 equiv. of *N*-methyl imine substrate.

ligand. Therefore, the cyclometallated ligand acts as a template for the H-bond-directed approach of the substrate. Using a novel methodology, the active cyclometallated catalyst **2** was synthesized and isolated as a crystalline air-stable solid. Complex **2** contains a triflate counterion and an acetonitrile solvent molecule that stabilizes the catalyst reactive site. X-ray analysis of **2** confirmed the structure of the catalyst and the correct position of the imide C=O groups to engage in an H-bond with the substrate. Finally, we have shown that the isolated catalyst provides the same activity and selectivity with respect the catalysts generated in situ with the BArF counterion, thereby suggesting that neither the triflate anion nor the acetonitrile ligand hamper the catalysis. ^{19}F NMR monitoring showed that the hydrogenation of 4'-(trifluoromethyl)acetophenone *N*-methyl imine catalyzed by complex **2** is very fast, with approx. 3500 h^{-1} TOF.

Supporting Information

Details of the DFT mechanistic studies, experimental procedures, spectroscopic data; ^{1}H NMR and ^{13}C NMR of all new compounds and chromatograms of racemic and enantioenriched amine products (PDF).

Acknowledgements

This work was supported by grants from FEDER/Ministerio de Ciencia e Innovación (MICINN) PID2020-115074GB-I00/AEI/10.13039/501100011033 (to A.R. and X.V.) and PID2020 116861GB-I00 (to A.L. and G.S.) and PID2020-117859RA-I00 and RYC2020-029099-I (to I.M.R). IRB Barcelona is the recipient of institutional funding from MICINN through the Centres of Excellence Severo Ochoa Award and from the CERCA Program of the Catalan Government. We thank Generalitat de Catalunya for grant 2021 SGR 00866. Calculations have been conducted using CSUC high-performance computing resources. This project received funding from the European Union's Horizon 2020 Research and Innovation Programme under the Marie Skłodowska-Curie Grant Agreement 101063517 (to J. E.). Y.W. thanks MICINN for a predoctoral fellowship. We thank Jordi Burés for insightful discussions on the kinetics of the process. We thank M. Bellido for the TOC graphic.

Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Asymmetric Hydrogenation · Iridium · Chiral at metal · Chiral amines · H-bonding

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[11] In situ hydrogenation of cyclohexylmethylketone *N*-phenyl imine with cyclometallating agent D produced the resulting amine with complete conversion and 63 % ee. This result suggests that the π–π interaction between substrate and catalysts is also crucial to attain high selectivity.

[12] Similar iridium dihydrides stabilized by coordinated solvent have been described in the literature, see: S. Gruber, M. Neuburger, A. Pfaltz, *Organometallics* **2013**, *32*, 4702–4711.

[13] Deposition number CCDC 2303279 (for **2**) contains 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.

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[15] Catalyst activity is greatly influenced by the structure of the imine substrate and reaction conditions. For instance, $>100000\ h^{-1}$ TOF is reported for the hydrogenation of the sterically hindered MEA imine in the metolachlor process, while the same catalytic system provides only $56\ h^{-1}$ with the cyclic imine 2,3,3-trimethyl-3H-indole (TMI), see: a) H.-U. Blaser, H.-P. Buser, R. Häusel, H.-P. Jalett, F. Spindler, *J. Organomet. Chem.* **2001**, *621*, 34–38; b) A. M. Kluwer, R. J. Detz, Z. Abiri, A. M. van der Burg, J. N. H. Reek, *Adv. Synth. Catal.* **2012**, *354*, 89–95. Non-asymmetric hydrogenation of **S18** with a cyclometallated Ir-catalyst has been reported with a TOF of $975\ h^{-1}$, see: c) Z.-J. Yao, N. Lin, X.-C. Qiao, J.-W. Zhu, W. Deng, *Organometallics* **2018**, *37*, 3883–3892. Most often reliable activity data is not reported for novel catalysts. To our knowledge, there is no TOF data on the hydrogenation of *N*-methyl imines with other catalysts.

[16] To assess the influence of the hydrogen pressure in the reaction outcome we measured the kinetic profile of the reaction at 6 bar of hydrogen (0.2 mM [cat] and 20 mM [imine]) and compared with the one at 3 bar (see SI). The reaction is faster, and it reaches completion in only 60s (TOF = $6000\ h^{-1}$). However, all efforts to reach 500 TON upon increasing the hydrogen pressure were not successful.

Manuscript received: March 12, 2024
Accepted manuscript online: April 19, 2024
Version of record online: May 21, 2024