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Grau de Química

Treball Final de Grau

Novel cyclometallated iridium catalysts for asymmetric hydrogenation of *N*-methyl and *N*-phenyl imines.

Nous catalitzadors ciclometal·lats d'iridi per hidrogenacions asimètriques d'*N*-metil i *N*-fenil imines.

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June 2019

Universitat de Barcelona

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Words are, in my not so humble opinion, our most inexhaustible source of magic, capable of both influencing injury, and remedying it.

Albus Dumbledore

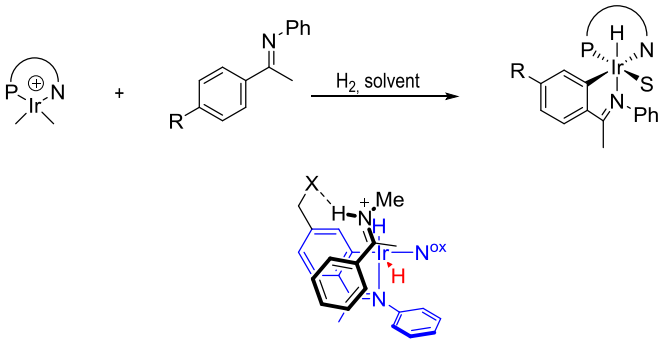
Primer de tot vull agrair als Profs. Antoni Riera i Xavier Verdaguer per haver-me donat la oportunitat de treballar al seu laboratori. He après molt i sempre han estat disposats a ajudar-me. Seguidament a l'Ernest, per haver-me aguantat tots aquests mesos, i a la resta de gent d'URSA, que m'ha agradat molt treballar amb ells.

REPORT

CONTENTS

1. SUMMARY

In this work, three acetophenone *N*-phenyl imine derivatives functionalized in the para position have been prepared and cyclometallated to Ir-MaxPHOX catalyst. One of the additives has a hydrogen bond acceptor group, while the others have bulky substituents. The behavior of these compounds in asymmetric hydrogenation of acetophenone *N*-methyl and *N*-phenyl imine substrates has been studied. The additive containing a hydrogen bond acceptor provided better enantioselectivity than the others. This reinforces the hypothesis that a hydrogen bond interaction between the catalyst and the substrate would increase the selectivity. Additives with bulky substituents provided worse results, probably due to steric hindrance, decreasing the selectivity.

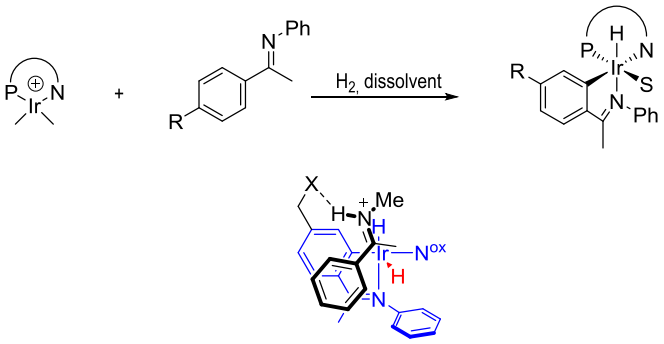


H-bond interaction

Keywords: Iridium, cyclometallation, imine asymmetric hydrogenation, hydrogen bond.

2. RESUM

En aquest treball s'han sintetitzat tres *N*-fenil imines derivades de l'acetofenona, funcionalitzades en la posició para, i s'han ciclometal·lat al catalitzador Ir-MaxPHOX. Un dels additius conté un grup acceptor de pont d'hidrogen, i la resta tenen substituents voluminosos. S'ha estudiat el comportament d'aquests compostos en la hidrogenació asimètrica de l'acetofenona *N*-metil i *N*-fenil imines. L'additiu amb el grup acceptor de pont d'hidrogen ha donat lloc a una millor enantioselectivitat que la resta. Això reforça la hipòtesi d'una interacció pont d'hidrogen entre el catalitzador i el substrat, que incrementaria l'excés enantiomèric. Els additius amb substituents impedits han produït pitjors resultats, probablement a causa de la repulsió estèrica, que fa disminuir la selectivitat.

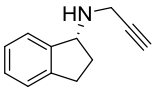


interacció pont d'H

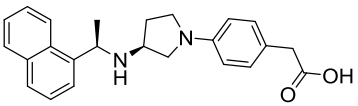
Paraules clau: Iridi, ciclometal·lació, hidrogenació asimètrica d'imines, pont d'hidrogen.

3. INTRODUCTION

Many chiral amines are important because of their biological activity. There are some examples, like Rasagline (for Alzheimer's treatment) or Evocalcet (for hyperparathyroidism and hypercalcemia).



Rasagiline



Evocalcet

Figure 1. Chiral amine drugs

Sometimes, one of the enantiomers show a biological activity while the other is not active or even toxic. That is why the asymmetric synthesis of this compounds or the corresponding precursors is very important. In an industrial scale, one of the best ways to obtain this type of compounds is the catalytic asymmetric hydrogenation of the corresponding imines.

3.1. IRIDIUM P,N CATALYSTS

3.1.1. Crabtree's catalyst

Iridium-P,N catalysts (Iridium coordinated to a bidentate or two monodentate ligands with P and N as donor atoms) have shown a very good selectivity in the hydrogenation of imines and alkenes. Crabtree was the first to introduce this type of catalyst, with a tricyclohexylphosphine and pyridine as ligands. This complex showed good behavior in alkene hydrogenation.

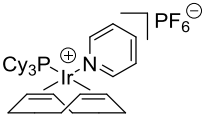


Figure 2. Crabtree's catalyst

3.1.2. Pfaltz's catalyst

Pfaltz was the first to introduce a chiral phosphino-oxazoline (PHOX) ligand. Also, the counteranion used was changed for a less coordinating BAr_F^- (tetrakis[3,5-bis(trifluoromethyl)-phenyl]borate). This catalyst gave good results hydrogenating *N*-aryl imines derived from aryl alkyl ketones[1]. However, when *N*-alkyl imines are hydrogenated, low conversions are observed. To understand this results, we need to understand the mechanism involved in this reaction.

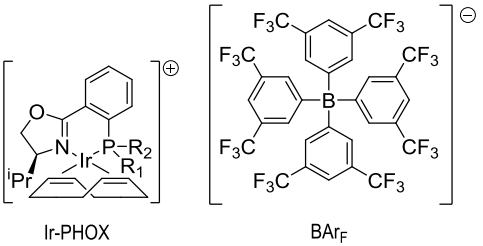
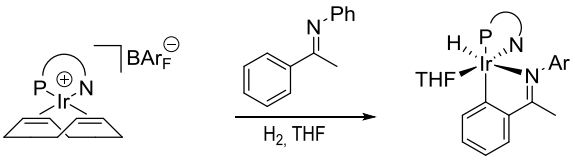


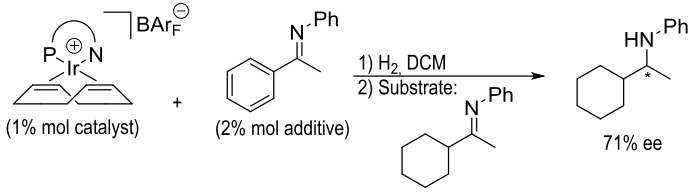
Figure 3. Pfalz catalyst

In 2013, Pfaltz and co-workers discovered that the catalyst in these reactions is not the Ir-P,N compound, but a cyclometallated complex (iridacycle) formed by coordination of imine nitrogen followed by a C-H activation of the orto carbon[2].



Scheme 1. Formation of Pfalz's iridacycle

As *N*-alkyl imines are different than *N*-aryl, the iridacycle formed also has different properties. In fact, attempts to synthesize an *N*-methyl imine iridacycle failed, but it has been achieved with the *N*-aryl compound. Also, as a C-H activation needs to happen, the imine must be derived from an aryl ketone. Despite dialkyl imines do not form an iridacycle, they can be hydrogenated by simply adding the substrate after forming the cyclometallated complex (Scheme 2).



Scheme 2. Dialkyl imine hydrogenation

3.1.3. Ir-MaxPHOX catalyst

The Ir-MaxPHOX catalyst is an Ir-P,N complex developed in our group. It contains an aminophosphine-oxazoline ligand, with 3 chiral centers and an R substituent that can be modified at will (figure 4a).

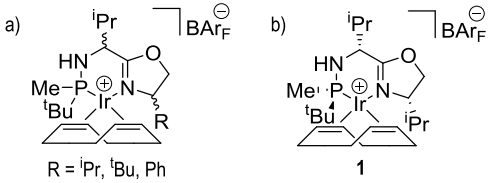
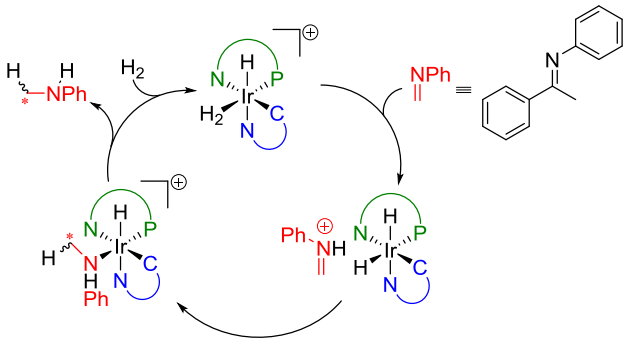


Figure 4. a) Ir-MaxPHOX general scaffold. b) Catalyst used in this work

The complex that have given best results in asymmetric hydrogenation of acetophenone imine derivatives is **1** with R = isopropyl with configuration *S*,*R*,*S*$_P$ (or *R*,*S*,*R*$_P$)[3,4] (figure 4b), and is the one used in this work.

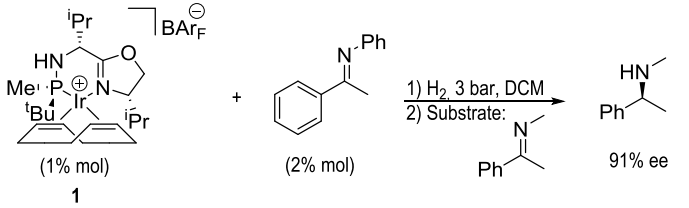
3.2. HYDROGENATION MECHANISM

Andersson and co-workers proposed a mechanism for the iridium-catalyzed imine hydrogenation[5] (Scheme 3). It is an outer sphere mechanism where the stereodetermining step is a hydride transfer to an iminium cation (the vacant position of the iridacycle is occupied by a hydrogen molecule).



Scheme 3. Hydrogenation mechanism

Recently, our group published that cyclometallated **1** catalyst is active and selective in the hydrogenation of *N*-methyl imines (scheme 4)[4].



Scheme 4. Asymmetric hydrogenation of *N*-methyl imines with cyclometallated **1** catalyst

A calculated structure for the transition states of acetophenone *N*-methyl imine that lead to both enantiomers of the product was also reported[4]. The most favorable transition state that leads to the major enantiomer is shown in figure 5.

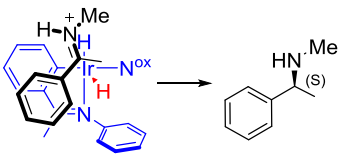


Figure 5. Most favorable TS leading to *S* enantiomer (in blue the iridacycle, in black the iminium cation, in red the hydride transferred)

Analyzing figure 5, we can see that the 4 position of the phenyl ring is near in space of the proton of iminium cation. To increase the selectivity, we thought about introducing a hydrogen

bond acceptor group in the para position of the aromatic ring, so it could interact with the iminium cation and favor the formation of the *S* enantiomer.

4. OBJECTIVES

- Synthesize and characterize new imine derivatives of acetophenone with hydrogen bond acceptor groups in para position (figure 6).
- Study the formation of an iridacycle with these new imines (additives).
- Use this iridacycles in asymmetric hydrogenation of the model substrates acetophenone *N*-methyl and *N*-phenyl imines.
- Synthesize (and isolate) iridacycles with different ligands in the vacant position.

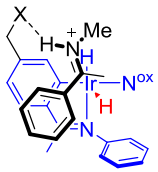
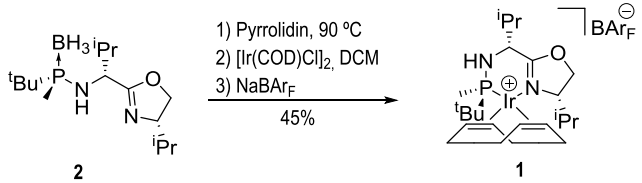


Figure 6. General idea of an iridacycle with an H bond acceptor group

5. SYNTHESIS OF IRIDIUM-MAXPHOX

To begin this work, the precatalyst **1** was synthesized by deprotection and coordination of the phosphino-oxazoline ligand **2** to $[IrCl(COD)]_2$, as shown in scheme 3.

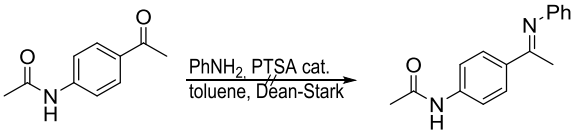


Scheme 3. Synthesis of the precatalyst **1**

After that, we proceeded with the synthesis of the imine.

6. INTRODUCING A HYDROGEN BOND ACCEPTOR GROUP

To make the H-bond interaction as strong as possible, we have to introduce a good hydrogen bond acceptor group. Amides are very good functional group for this purpose because of delocalization of the nitrogen lone pair of electrons to oxygen. We first tried with 4-acetamido acetophenone, but we could not prepare the corresponding imine due to solubility problems.

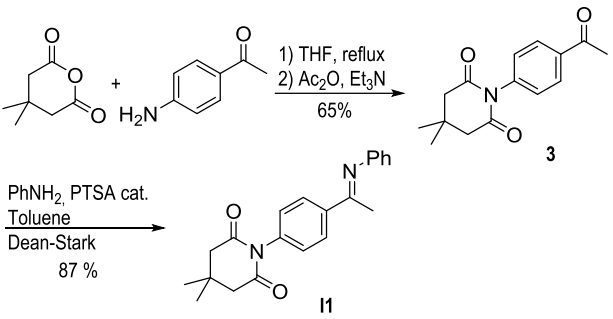


Scheme 4. Synthesis of imine **I1**

We next thought about, using a six-membered ring imide, with two methyl substituents that would increase the solubility.

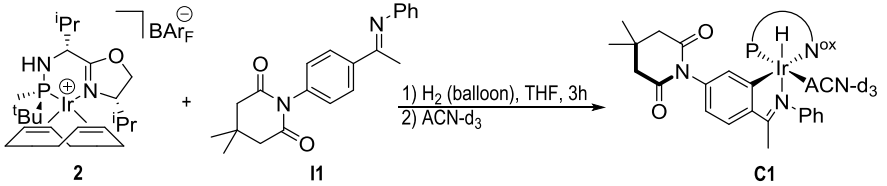
6.1. SYNTHESIS AND IRIDACYCLE ANALYSIS

The ketone precursor was prepared in 2 steps as described in scheme 5. Then, with a Dean-Stark azeotropic distillation the imine **I1** was synthesized. It also could be isolated by trituration with Et_2O. The final imine was slightly unpurified with starting ketone and aniline.



Scheme 5. Synthesis of imine **I1**

With this imine, we analyzed the formation of an iridacycle. To do so, the cyclometallation was carried out in THF and then acetonitrile-d_3 was added to coordinate the vacant position (scheme 6).



Scheme 6. Synthesis of iridacycle **C1**

The presence of the iridacycle is confirmed by ^{1}H- and ^{31}P-NMR. The hydride and the phosphorus must be a doublet (figure 6).

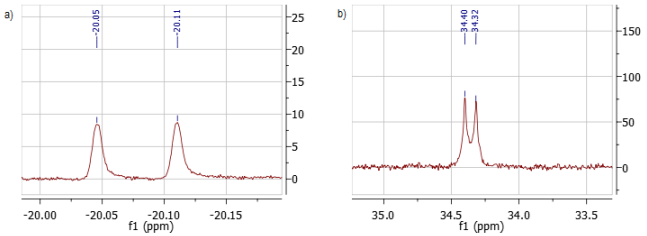
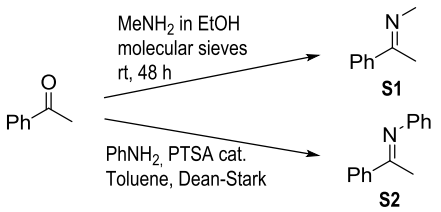


Figure 6 a) ^{1}H-NMR (hydride zone). B) ^{31}P-NMR of complex **C1** (expanded)

The next thing we did was to use this iridacycle in asymmetric hydrogenations.

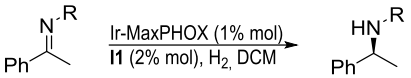
6.2. ASYMMETRIC HYDROGENATION OF IMINES

Out of all possible imine substrates we choose the methyl and phenyl imines of acetophenone. Both molecules were synthesized as described in scheme 7.



Scheme 7. Synthesis of substrates **S1** and **S2**

N-alkyl imines are not very reactive, so hydrogenations must be carried out at 3 bar of hydrogen pressure, otherwise full conversions will not be observed. However, *N*-aryl imines are more reactive and can be hydrogenated at atmospheric pressure (balloon). The results are depicted in table 1.



Entry	R	H_2 [bar]	T [ºC]	Conv. [%][b]	ee [%][c]
1	Me	3	rt	100	95
2	Me	3	0	100	94
3	Ph	balloon	rt	100	95
4	Ph	balloon	0	100	96
5	Ph	balloon	-20	100	96

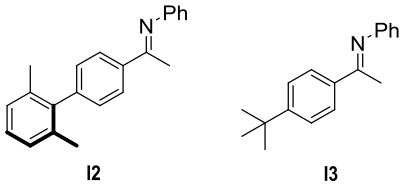
(a) All reactions were left overnight.
(b) Conversions were determined by ^{1}H-NMR.
(c) Enantiomeric excesses were determined by chiral HPLC (methyl amines were trifluoroacetilated before HPLC analysis).

Table 1. Results of asymmetric hydrogenations using additive **I1.**

The results obtained with methyl imines are better than the ones previously reported by our group (91% ee)[4]. However, the enantioselectivity did not increase at lower temperatures as we expected. On the other hand, phenyl imines gave the same results reported previously, but while we needed -20 ºC to afford a 96% ee[3], we have obtained the same result at 0 ºC.

7. INTRODUCING BULKY GROUPS

To confirm that a hydrogen bond interaction is responsible for the increased selectivity and not the steric repulsion of the glutarimido ring, we synthesized two more additives with a bulky group in the para position lacking a H-bond acceptor. These new groups are a *tert*-butyl and a 2,6-dimethylphenyl (figure 7).



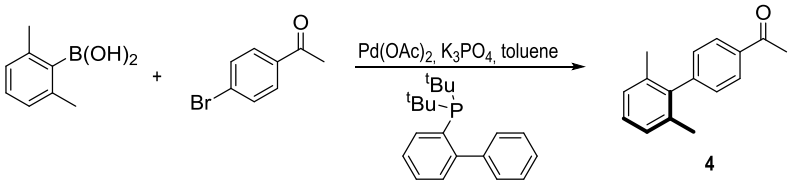
I2 **I3**

Figure 7. New additives with bulky substituents

The new iridacycles would make a repulsion interaction with the iminium cation, just like the imide iridacycle could do. If we obtain worse results with these new additives, it would confirm the hypothesis that there is a hydrogen bond interaction between the iridacycle and the substrate.

7.1. SYNTHESIS AND IRIDACYCLE ANALYSIS

The ketone precursor of **I2** was synthesized with a Suzuki coupling of the corresponding boronic acid and aryl bromide (scheme 8). The *tert*-butyl analog was not prepared as it is commercially available.

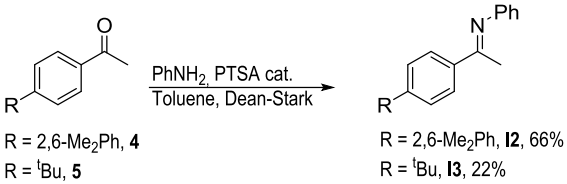


4

41%

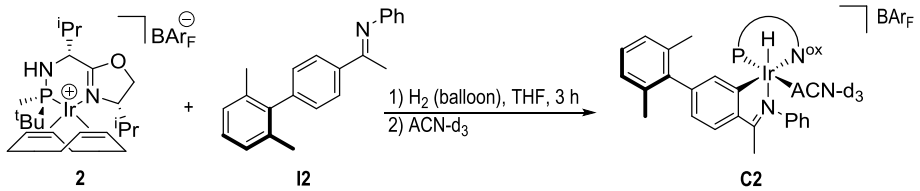
Scheme 8. Synthesis of precursor **4**

Then, both imines were synthesized. The biphenyl imine was easily purified by crystallization, while the other was distilled under vacuum.



Scheme 9. Synthesis of bulky imines

With the new imines prepared in hand, we proceeded with the analysis of the corresponding iridacycles. As the imine **I3** was already used by Pfaltz[2], we only analyzed the formation of iridacycle **C2** (scheme 10).



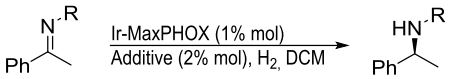
Scheme 10. Synthesis of iridacycle **C2**

The NMR spectra's showed the same signals as we had obtained previously with iridacycle **C1**, confirming the presence of the iridacycle, and that a single isomer was formed.

We next proceeded with the hydrogenations.

7.2. ASYMMETRIC HYDROGENATION OF IMINES

The same imines as before were hydrogenated, at different hydrogen pressure and temperatures (table 2).



Entry	Additive	R	H_2 [bar]	T [ºC]	Conv. [%][b]	ee [%][c]
1	**I2**	Me	3	rt	100	69
2	**I2**	Ph	balloon	rt	100	73
3	**I3**	Me	3	rt	100	91
4	**I3**	Me	3	0	100	93
5	**I3**	Ph	balloon	rt	100	82
6	**I3**	Ph	balloon	-20	97	90

(a) All reactions were left overnight.
(b) Conversions were determined by ^{1}H-NMR.
(c) Enantiomeric excesses were determined by chiral HPLC (methyl amines were trifluoroacetilated before HPLC analysis).

Table 2. Results of asymmetric hydrogenations using additives **I2** and **I3**

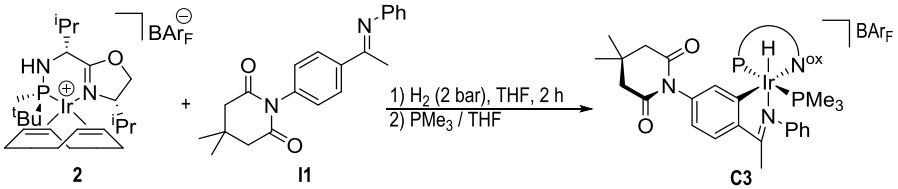
I2 provided very low selectivity with both substrates. On the other hand, *tert*-butyl additive (**I3**) provided better results. With *N*-methyl imine we obtained 93% ee, higher than 91% ee reported previously[4], but still it does not improve the 95% ee obtained with **I1**. For *N*-phenyl imines, the results do not represent an improvement with respect the results reported[4] for **I1**.

The fact that additive **I1** afforded better enantiomeric excesses, reinforces the hypothesis of a hydrogen bond interaction between the cyclometallated imine and the substrate. With this in mind, we plan to synthesize more additives with other hydrogen bond acceptor groups and see the behavior in *N*-alkyl and *N*-aryl imine hydrogenation. Also, a screening of solvents could be interesting to see which is better for this type of reactions.

8. DETERMINING THE STRUCTURE OF THE IRIDACYCLE

After knowing which was the best additive, we proceeded to the crystallization of the iridacycle, to obtain an X-Ray structure. As it has been reported previously in our group[4], crystals can be obtained by occupying the vacant position of the complex by a stabilizing ligand like PMe_3.

The iridacycle with this phosphine ligand was synthesized as shown in scheme 11, and crystallization is ongoing.



Scheme 11. Synthesis of iridacycle **C3**

The presence of this compound was confirmed by ^1H- and ^{31}P-NMR spectra. The hydride resonance is a triplet due to coupling with the two phosphorus, while two doublets appear in the ^{31}P-NMR spectra.

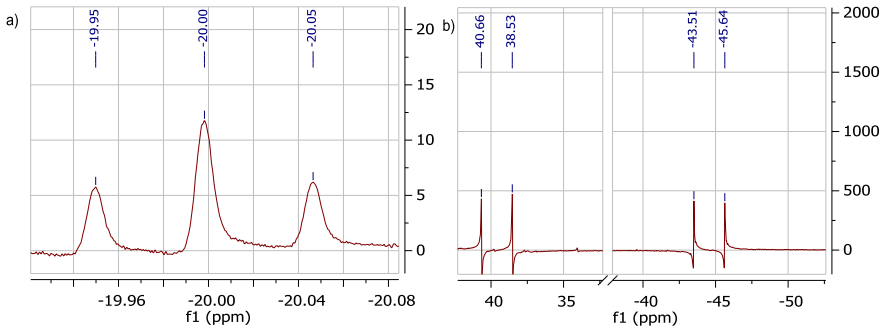


Figure 8 a) ^1H-NMR (hydride zone). b) ^{31}P-NMR of complex **C3**

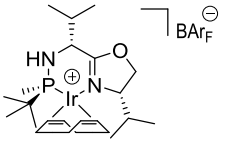
9. EXPERIMENTAL SECTION

9.1. MATERIALS AND METHODS

All reactions were carried out under nitrogen atmosphere in dried solvents. THF and Et_2O were dried in a PureSolv purification system from Innovative Technology, Inc. Other commercially available reagents and solvents were used with no further purification. Thin layer chromatography was carried out using TLC-aluminum sheets with silica gel (Merk 60 F_{254}). Silica gel chromatography was performed by using 35-70 mm silica or an automated chromatography system (Combiflash®, Teledyne Isco) with hexanes/ethyl acetate gradients as eluent unless noted otherwise. NMR spectra were recorded at 23 °C on Varian Mercury 400 or Varian 500 apparatus. ^{1}H NMR and ^{13}C NMR spectra were referenced either to relative internal TMS or to residual solvent peaks. ^{31}P NMR spectra were referenced to phosphoric acid. Melting points were determined using a Büchi melting point apparatus and were not corrected. IR spectra were recorded in a Thermo Nicolet Nexus FT-IR apparatus. HRMS were recorded in a LTQ-FT Ultra (Thermo Scientific) using Nanoelectrospray technique. HPLC chromatography was performed on an Agilent Technologies Series 1100 chromatograph with UV detector.

9.2. PREPARATION OF Ir-MaxPHOX CATALYST (1)

A 25 mL Schlenk flask was charged with 50 mg (0.167 mmol, 1 eq) of aminophosphino-oxazoline ligand and was connected to the vacuum for 1 h. Then, it was charged with nitrogen (balloon) and 3 mL of pyrrolidine were added. The mixture was heated at 90 ºC overnight. The following day, the system was cooled down to room temperature and the pyrrolidine was removed in vacuum and heating at 50 ºC. 56 mg (0.084 mmol, 0.5 eq) of $[Ir(COD)Cl]_2$ dissolved in DCM (1 mL) was added and the system was left stirring for 3 hours. Afterwards, 148 mg (0.167 mmol, 1 eq) of sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate ($NaBAr_F$) were added and the solution was stirred for 1 hour. Then, the solvents were removed under reduced pressure and the product was purified by silica column to afford 109 mg (45%) of an orange solid.

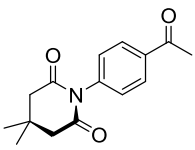


Orange solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.78 – 7.66 (m, 8H), 7.53 (s, 4H), 5.14 – 5.02 (m, 1H), 4.92 – 4.81 (m, 1H), 4.48 (dd, *J* = 9.7, 4.2 Hz, 1H), 4.27 (t, *J* = 9.8 Hz, 1H), 4.09 – 4.00 (m, 1H), 3.77 – 3.67 (m, 1H), 3.63 – 3.54 (m, 1H), 3.40 (ddd, *J* = 20.9, 9.9, 7.1 Hz, 1H), 2.74 (dt, *J* = 9.6, 6.2 Hz, 1H), 2.32 – 2.11 (m, 5H), 2.08 (d, *J* = 10.2 Hz, 2H), 1.99 – 1.74 (m, 3H), 1.34 (d, *J* = 7.7 Hz, 3H), 1.09 (s, 9H), 0.99 (d, *J* = 6.7 Hz, 3H), 0.98 (d, *J* = 6.5 Hz, 3H), 0.88 (d, *J* = 7.2 Hz, 3H), 0.86 (d, *J* = 6.9 Hz, 3H) ppm.
This compound is described in the literature.[6]

9.3. SYNTHESIS OF IMINE ADDITIVES

9.3.1. Synthesis of *p*-(3,3-dimethylglutarimido)acetophenone (3)

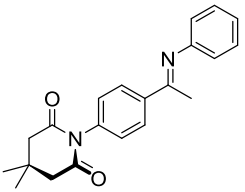
A 100 mL round bottom flask was charged with 2.6 g (18.3 mmol, 1 eq) of 3,3-dimethyl-glutaric anhydride and 2.6 g (19.2 mmol, 1.05 eq) of 4-aminoacetophenone and was purged with nitrogen/vacuum cycles. Dry THF (30 mL) was added and the solution was left at reflux overnight. The following day, the system was cooled down to room temperature and the solvent was removed in a rotatory evaporator. The orange ropy oil obtained was dissolved in EtOAc and transferred into a separatory funnel. It was washed with HCl 1M (some precipitate was formed and was dissolved after adding more ethyl acetate), the organic phase was dried with $MgSO_4$ and the solvent was evaporated under reduced pressure to afford a pale yellow solid that was treated neat with 5.2 mL of acetic anhydride (54.9 mmol, 3 eq) and 3.8 mL of triethylamine (27.5 mmol, 1.5 eq). The mixture was heated at 80 ºC for 3 hours. After that time, the system was cooled down to room temperature and the solvent was evaporated under reduced pressure. The solid obtained was dissolved in ethyl acetate and washed with HCl 1M and saturated $NaHCO_3$. The organic layer was dried with magnesium sulfate and the solvent was removed to obtain 3 g (65%) of a pale orange solid.



Pale orange solid. Mp: 153.3-155.5 ºC. IR (KBr): 3049, 2950, 1688, 1681, 1600 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.05 (d, *J* = 8.5 Hz, 2H), 7.24 – 7.16 (m, 2H), 2.69 (s, 4H), 2.62 (s, 3H), 1.23 (s, 6H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ: 197.2 (C), 171.8 (C), 139.4 (C), 137.1 (C), 129.4 (CH), 129.0 (CH), 46.7 (CH_2), 29.5 (C), 27.9 (CH_3), 26.8 (CH_3) ppm. HRMS (ESI): calc. for $[C15H17NO3+H]^+$: 260.1281, found: 260.1280.

9.3.2. Synthesis of *p*-(3,3-dimethylglutarimido)acetophenone *N*-phenyl imine (I1)

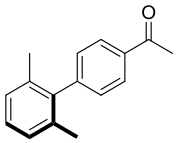
A 50 mL round-bottom flask was charged with 1 g of *p*-(3,3-dimethylglutarimido)-acetophenone, 1.40 mL (15.4 mmol, 4 eq) of aniline and 15 mg (0.077 mmol, 0.02 eq) of *p*-toluenesulfonic acid. The system was equipped with a Dean-Stark and purged with nitrogen/vacuum cycles. Then, 30 mL of toluene were added and it was left stirring at reflux overnight under N_2. The next day the system was cooled down to room temperature and sodium carbonate (41 mg, 0.39 mmol, 0.1 eq) was added and after 5 minutes stirring the mixture was filtered and the solvents evaporated under reduced pressure. The resulting crude was triturated with ether to dissolve the impurities and after filtration 1.03 g (79%) of a white yellowish solid was obtained. ^{1}H-NMR analysis showed 87% purity with come starting materials present in the product.



White yellowish solid. Mp: 186.4-189.7 ºC. IR (KBr): 2949, 1678, 1589, 1369 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.11 – 8.06 (m, 2H), 7.35 (dd, *J* = 8.3, 7.4 Hz, 2H), 7.20 – 7.15 (m, 2H), 7.12 – 7.07 (m, 1H), 6.81 – 6.76 (m, 2H), 2.70 (s, 4H), 2.24 (s, 3H), 1.23 (s, 6H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ: 171.9 (C), 164.5 (C), 151.6 (C), 139.6 (C), 137.1 (C), 129.1 (CH), 128.6 (CH), 128.3 (CH), 123.5 (CH), 119.4 (CH), 46.7 (CH_2), 29.5 (C), 27.9 (CH_3), 17.4 (CH_3) ppm. HRMS (ESI): calc. for $[C_{21}H_{22}N_2O_2+H]^+$: 335.1754, found: 335.1757.

9.3.3. Synthesis of *p*-(1,3-dimethylphenyl)acetophenone (4)

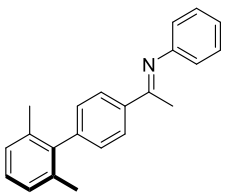
A 250 mL purged Shclenk flask was charged with 0.3 g (1 mmol, 0.04 eq) of di-*tert*-butyl(2-phenylphenyl)phosphine, 5.65 g (37.68 mmol, 1.5 eq) of 2,6-dimethylphenyl boronic acid, 112 mg (0.5 mmol, 0.02 eq) of $Pd(OAc)_2$, 10.66 g of K_3PO_4 (50.25 mmol, 2 eq), 5 g (25.12 mmol, 1 eq) of 4-bromo acetophenone and 75 mL of toluene. The mixture was left stirring overnight at 85 ºC. The following day the system was cooled down to room temperature, dissolved in diethyl ether (30 mL) and washed with NaOH 40%. The organic layer was next washed with brine, dried with magnesium sulphate and the solvent evaporated under reduced pressure. The product obtained was purified by column chromatography (hexane/EtOAc) to afford 2.3 g (41%) of a brown solid.



Brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.07 – 8.00 (m, 2H), 7.29 – 7.24 (m, 2H), 7.22 – 7.16 (m, 1H), 7.14 – 7.10 (m, 2H), 2.66 (s, 3H), 2.02 (s, 6H) ppm.
This compound is described in the literature.[7]

9.3.4. Synthesis of *p*-(1,3-dimethylphenyl)acetophenone *N*-phenyl imine (I2)

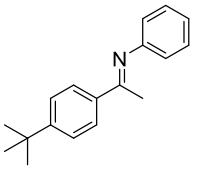
In a 100 mL round bottom flask equipped with a Dean-Stark, 2.33 g of 4-(2,6-dimethylphenyl)acetophenone (10.38 mmol, 1 eq), 1.42 mL of aniline (15.58 mmol, 1.5 eq) and 40 mg of PTSA (0.21 mmol, 0.02 eq) were added and the system was purged with N_2. Then, toluene (50 mL) was added and the solution was heated at reflux overnight. The following day, the system was cooled down to room temperature and 0.15 g of sodium carbonate (1.41 mmol, 6.7 eq) were added. The mixture was stirred during 5 minutes. Then it was filtered and the solvents were evaporated under reduced pressure. The resulting oil was purified by crystallization with hexane to afford 2.06 g (66%) of product as a yellowish-white solid.



Yellowish-white solid. Mp: 97.7-98.7 ºC. IR (ATR): 3036, 2955, 1630, 1587 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.10 – 8.05 (m, 2H), 7.43 – 7.33 (m, 2H), 7.26 (s, 2H), 7.22 – 7.08 (m, 4H), 6.84 (m, *J* = 7.5, 1.0 Hz, 2H), 2.30 (s, 3H), 2.07 (s, 5H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ: 165.5 (C), 151.9 (C), 143.7 (C), 141.3 (C), 138.0 (C), 136.0 (C), 129.3 (CH), 129.1 (CH), 127.5 (CH), 127.4 (CH), 123.4 (CH), 119.6 (CH), 21.0 (CH_3), 17.5 (CH_3) ppm. HRMS (ESI): calc. for $[C22H21N+H]^+$: 300.1747, found: 300.1742.

9.3.5. Synthesis of *p*-(*tert*-butyl)acetophenone *N*-phenyl imine (I3)

A 250 mL round-bottom flask equipped with a Dean-Stark was charged with 5 g (28.4 mmol, 1 eq) of 4-*tert*-butyl acetophenone, 7.8 ml (85.11 mmol, 3 eq) of aniline and 108 mg (0.57 mmol, 0.02 eq) of PTSA. The system was purged with nitrogen/vacuum cycles and toluene (125 ml) was added. The mixture was heated at reflux overnight. The following day 300 mg of Na_2CO_3 (2.83 mmol, 0.1 eq) was added and after stirring for 5 minutes the solution was filtered and the solvent was eliminated under reduced pressure. The crude obtained was purified by Kugelrohr distillation (224 ºC, 0.1 mbar) to afford 1.55 g (22%) of a yellow crystalline solid.



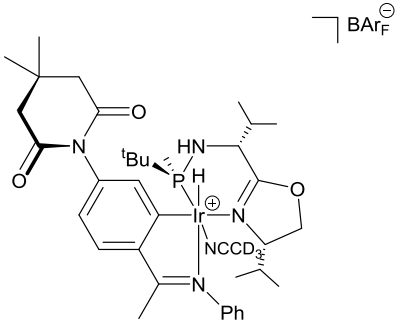
Yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.96 – 7.90 (m, 2H), 7.51 – 7.44 (m, 2H), 7.39 – 7.31 (m, 2H), 7.08 (tt, *J* = 7.5, 1.2 Hz, 1H), 6.83 – 6.76 (m, 2H), 2.23 (s, 3H), 1.36 (d, *J* = 0.6 Hz, 9H) ppm.
This compound is described in the literature[2].

9.4. PREPARATION OF IRIDACYCLES

9.4.1. General Method for iridacycle formation analysis

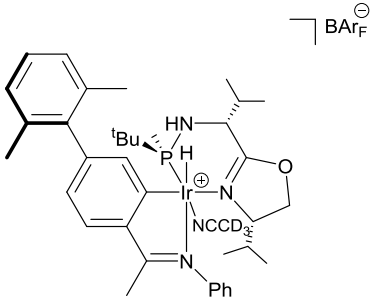
10 mg (0.0069 mmol, 1 eq) of Ir-MaxPHOX catalyst and the corresponding imine (0.0138 mmol, 2 eq) were placed in a 25 mL Schlenk flask and the system was purged with nitrogen/vacuum cycles. Dry THF (1.5 mL) was added and the flask was purged with hydrogen at atmospheric pressure and it was left stirring for 3 hours. After that time, ACN-d_3 (0.75 mL) was added and after 30 minutes the solvents were eliminated under reduced pressure. The resulting orange solid was dissolved 0.75 mL of ACN-d_3 and analyzed by ^{1}H- and ^{31}P-NMR in nitrogen atmosphere.

9.4.2. Imide iridacycle (C1)



^{1}H NMR (400 MHz, CD_3CN) δ: 0.68 (d, J = 6.8 Hz, 3H), 0.62 (d, J = 14.9 Hz, 9H), -20.00 (d, J = 25.8 Hz, 1H) ppm. ^{31}P NMR (162 MHz, CD_3CN), δ: 34.36 (d, J = 13.2 Hz) ppm.

9.4.3. *p*-dimethylphenyl acetophenone *N*-phenyl imine iridacycle (C2)

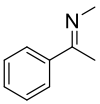


^{1}H NMR (400 MHz, CD_3CN) δ: 0.69 (d, *J* = 14.8 Hz, 9H), 0.67 (d, *J* = 6.7 Hz, 3H), -19.90 (d, *J* = 26.0 Hz, 1H) ppm. ^{31}P NMR (162 MHz, CD_3CN) δ: +34.74 (d, *J* = 23.9 Hz) ppm.

9.5. SYNTHESIS OF IMINE SUBSTRATES

9.5.1. Acetophenone *N*-methyl imine (S1)

10 g of activated molecular sieves (dust, 4 Å) were placed in a 100 mL Schlenk flask and then the flask was purged with N_2. Acetophenone (4.7 mL, 1 eq) and methyl amine in ethanol (30 mL, 33% wt., 6 eq) were added and the mixture was left stirring for 48 h at room temperature. The suspension obtained was filtered through celite and washed with DCM. The solvents were evaporated to afford a pale-yellow oil that was purified by Kugelrohr distillation (50 ºC, 0.1 mbar) to obtain 3.4 g (65 %) of a colorless oil.

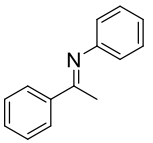


^{1}H NMR (400 MHz, $CDCl_3$). E/Z ratio = 94:6. Major isomer δ: 7.79 – 7.72 (m, 2H), 7.42 – 7.34 (m, 3H), 3.35 (d, *J* = 0.9 Hz, 3H), 2.24 (q, *J* = 0.9 Hz, 3H) ppm.

9.5.2. Acetophenone *N*-phenyl imine (S2)

In a 100 mL round bottom flask equipped with a Dean-Stark, acetophenone (4 ml, 1 eq), aniline (3.2 mL, 1.05 eq) and PTSA (65.3 mg, 0.01 eq) were added and the system was purged with N_2. Then, toluene (50 mL) was added and the solution was heated at reflux overnight. The following day the system was cooled down to room temperature and sodium carbonate (110 mg, 0.06 eq) was added. The mixture was stirred for 5 minutes. Then it was filtered and the

solvents were evaporated under reduced pressure. The orange oil obtained was purified by Kugelrohr distillation (190 ºC, 0.1 mbar) to afford 4.3 g (64 %) of a yellowish solid.

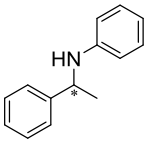


^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.03 – 7.94 (m, 2H), 7.49 – 7.41 (m, 3H), 7.39 – 7.32 (m, 2H), 7.09 (m, 1H), 6.83 – 6.77 (m, 2H), 2.24 (s, 3H) ppm.

9.6. HYDROGENATION OF *N*-METHYL AND *N*-PHENYL IMINES

9.6.1. GM: *N*-phenyl imine hydrogenation with Ir-MaxPHOX iridacycles

In a 25 mL Schlenk flask 5 mg (0.01 eq) of Ir-MaxPHOX 1-^{i}Pr and the corresponding imine additive (0.02 eq) were added. Then, the flask was purged with N_2 and DCM anhydrous (2 mL) was added. The system was purged with H_2 (balloon) and stirred for 30 minutes at rt (if the reaction was carried out at low temperatures, it was stirred at room temperature for 20 minutes and then was cooled down to the desired temperature for 10 minutes). After that time, the substrate (1 eq) dissolved in anhydrous DCM (1 mL) was added dropwise to the reaction mixture and it was left stirring overnight. The following day the hydrogen was released (at low temperatures, while the flask was cool) and the solution was filtered through silica. Finally, the solvent was removed under reduced pressure to afford the hydrogenated compounds as brown oils.

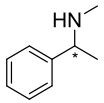


Brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.42 – 7.28 (m, 4H), 7.25 – 7.20 (m, 1H), 7.14 – 7.06 (m, 2H), 6.69 – 6.62 (m, 1H), 6.55 – 6.50 (m, 2H), 4.49 (q, *J* = 6.7 Hz, 1H), 1.53 (d, *J* = 6.7 Hz, 3H) ppm. HPLC (CHIRALCEL OD-H, heptane / ^{i}PrOH 90:10, 1 mL / min, λ = 220 nm): tR(+) = 15.4 min, tR(−) = 17.0 min

9.6.2. GM: *N*-methyl imine hydrogenation with Ir-MaxPHOX iridacycles

In a glass pressure tube 5 mg (0.01 eq) of Ir-MaxPHOX 1-^{i}Pr and the corresponding imine additive (0.02 eq) were added. Then, the tube was purged with N_2 (vacuum-nitrogen cycles) and DCM anhydrous (2 mL) was added. The system was purged with H_2 at 3 bar (vacuum-hydrogen cycles) and stirred 30 minutes at rt (if the reaction was carried out at low temperatures, it was stirred at room temperature for 20 minutes and then was cooled down to the desired

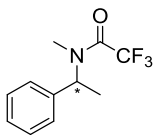
temperature for 10 minutes). After that time, the substrate (1 eq) dissolved in anhydrous DCM (1 mL) was added dropwise to the reaction mixture using a pressure syringe and it was left stirring overnight. The following day the hydrogen was released (at low temperatures, while the flask was still cool) and the solvent was evaporated under reduced pressure to afford the hydrogenated compounds as brown oils. The ee was determined by chiral HPLC of the corresponding trifluoroacetamide.



Brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.36 – 7.28 (m, 4H), 7.25 – 7.22 (m, 1H), 3.65 (q, *J* = 6.6 Hz, 1H), 2.31 (s, 3H), 1.37 (d, *J* = 6.6 Hz, 3H) ppm.

9.6.3. GM: trifluoroacetylation of *N*-methyl amines

The crude of the corresponding hydrogenation was placed in a 10 mL round bottom flask with 2 mL of DCM. Then, 0.11 mL of pyridine (4 eq) and 0.10 mL of trifluoroacetic anhydride (2 eq) were added and the mixture was left stirring for 2 hours. After that time, 2 mL of water were added to quench the reaction. The organic phase was washed with water, dried with $MgSO_4$ and concentrated under reduced pressure. The resulting oil was purified by column chromatography to afford the product as a colorless oil.



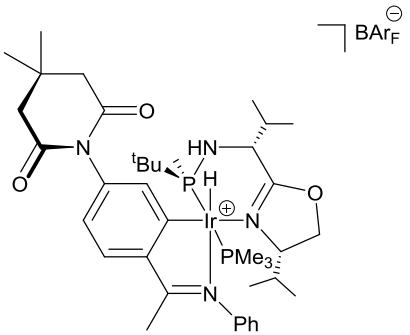
Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.39 – 7.23 (m, 5H), 5.91 (q, *J* = 7.1 Hz, 1H), 2.74 (q, *J* = 1.7 Hz, 3H), 1.53 (d, *J* = 7.1 Hz, 3H) ppm.
HPLC: CHIRALCEL OD- H. Heptane / ^{i}PrOH 98:02, 0.5 mL / min, λ = 210 nm. t_S(–)= 13.4 min, t_R(+)=14.7 min.

9.6.4. GM: racemic hydrogenation of *N*-methyl and *N*-phenyl imines.

A 10 mL round-bottom flask was charged with the corresponding imine (1 eq) and methanol (1 mL / 25 mg of imine). The system was placed in an ice bath and sodium borohydride (3 eq) was added. After 10 minutes, the solution was cooled down to room temperature and was left stirring overnight. The following day, brine was added to quench the solution and then was transferred into a separatory funnel. Extractions with ethyl acetate were made and the organic layers were collected, dried with $MgSO_4$ and the solvent was removed in a rotatory evaporator to afford the corresponding imines as a colorless oil.

9.7. SYNTHESIS OF TRIMETHYLPHOSPHINE IRIDACYCLE (C3)

A Schlenk tube was charged with 50 mg (0.035 mmol, 1 eq) of Ir-MaxPHOX and 23.1 mg (0.069 mmol, 2 eq) of *p*-(3,3-dimethylglutarimido)acetophenone *N*-phenyl imine and purged with nitrogen-vacuum cycles. Anhydrous THF (3 mL) was added and the solution was transferred into a Fischer-Porter tube, it was charged with hydrogen at 2 bar and was left stirring for 2 hours. After that time the mixture was transferred into a Schlenk tube and PMe_3/THF (0.5 mL, 1 M) was added. After 30 minutes of the addition the solvents were evaporated under reduced pressure and the orange solid obtained was washed with pentane and purified by silica column chromatography (Et_2O/DCM) to afford 30 mg (55%) of a pale orange solid.



Pale orange solid. Yield: 55% (30 mg). ^{1}H NMR (400 MHz, CD_2Cl_2) δ: 7.75 – 7.71 (m, 10H), 7.56 (s, 4H), 7.50 – 7.42 (m, 2H), 7.37 (t, *J* = 1.8 Hz, 2H), 7.31 (tt, *J* = 7.5, 1.2 Hz, 1H), 6.96 (s, 1H), 6.91 – 6.86 (m, 1H), 4.42 – 4.35 (m, 1H), 4.16 – 4.04 (m, 2H), 2.78 (td, *J* = 9.6, 5.0 Hz, 1H), 2.64 (s, 5H), 1.83 (ddd, *J* = 8.4, 2.2, 1.1 Hz, 3H), 1.77 – 1.65 (m, 1H), 0.93 (d, *J* = 7.1 Hz, 3H), 0.78 (d, *J* = 6.8 Hz, 3H), 0.69 (d, *J* = 6.8 Hz, 3H), 0.63 (d, 2H), 0.60 (d, *J* = 14.5 Hz, 9H), -20.00 (t, *J* = 19.4 Hz, 1H) ppm. ^{31}P NMR (162 MHz, CD_2Cl_2) δ: +39.60 (d, *J* = 345.0 Hz), -44.57 (d, *J* = 344.7 Hz) ppm.

10. CONCLUSIONS

We have synthesized three *N*-phenyl imines derived from acetophenone, one with an H-bond acceptor, and the others with bulky groups. All this additives have been coordinated to Ir-MaxPHOX and have been used in asymmetric hydrogenation of acetophenone *N*-methyl and *N*-phenyl imines. The hydrogen bond additive provided the best enantiomeric excess reported until now for direct asymmetric hydrogenation of *N*-alkyl imines (95%), while the other additives do not represent an improvement in the selectivity of this reaction. These results reinforce our theory of a hydrogen bond interaction in the transition state, between the iminium cation and the catalyst.

We also have tried to synthesize and crystallize an iridacycle with the hydrogen bond additive, by coordinating the stabilizing ligand PMe_3, this last part is still on going.

11. REFERENCES AND NOTES

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12. ACRONYMS

ACN	Acetonitrile
Ar	Aryl
BAr_F	tetrakis[3,5-bis(trifluoromethyl)phenyl]borate
COD	1,5-cyclooctadiene
Cy	Cyclohexyl
DCM	Dichloromethane
PTSA	p-toluenesulfonic acid
THF	Tetrahydrofuran