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Communication

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Direct Asymmetric Hydrogenation of *N*-Methyl and *N*-Alkyl Imines with an Ir(III)H Catalyst

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Supporting Information Placeholder

ABSTRACT: A novel cationic [IrH(THF)(P,N)(imine)] [BAr_F] catalyst containing a *P*-stereogenic MaxPHOX ligand is described for the direct asymmetric hydrogenation of *N*-methyl and *N*-alkyl imines. This is the first catalytic system to attain high enantioselectivity (up to 94% ee) in this type of transformation. The labile THF ligand allows for effective activation and reactivity, even at low temperatures. DFT calculations allowed the rationalization of the stereochemical course of the reaction.

Chiral *N*-methyl or *N*-alkyl amine is a frequent pharmacophore in pharmaceutical substances (Figure 1). Examples include sertraline (to treat depression),[1] dextro-methamphetamine (to treat ADHD and narcolepsy),[2] rivastigmine (to treat Alzheimer's and Parkinson's diseases)[3] and cinacalcet (to treat hyperparathyroidism).[4] Due to the importance of this moiety, many efforts have been devoted to the asymmetric synthesis of optically pure *N*-methyl amines.[5] An ideal methodology to obtain this class of compounds is the catalytic reduction of the corresponding imines. However, the high basicity and nucleophilicity of *N*-methyl amines often results in catalyst deactivation. The most successful approaches for the asymmetric reduction of *N*-methyl imines are Ti-catalyzed hydrosilylation, reported by Buchwald,[6a] and Brönsted acid-catalyzed reduction using Hantzsch ester in the presence of Boc_2O, reported by List.[6b] In both cases, the final amine product is protected with either a SiR_3 or Boc group, thus circumventing the basicity issue associated with the free amine.

From an industrial perspective, the direct hydrogenation of imines is a much more desirable process;[7] however, in contrast to the good results obtained with *N*-aryl ketimines,[8,9] the hydrogenation of *N*-methyl ketimines has not yet been achieved with useful levels of enantioselectivity. Pfaltz and co-workers reported the hydrogenation of the *N*-methyl imine of acetophenone with Ir-PHOX catalysts, achieving only 58% ee (Scheme 1).[10] The conversion was complete, but harsh pressures of hydrogen (100 bar) and high catalyst loadings (4 mol%) were required. We hypothesize that this difference between *N*-aryl and *N*-alkyl ketimines is due to the aforementioned basicity of this class of compounds. Here we report a novel type of Ir(III) precatalyst that can be used directly in hydrogenation reactions and that has allowed the direct hydrogenation of *N*-methyl and *N*-alkyl imines in mild conditions and with high levels of selectivity (Scheme 1).

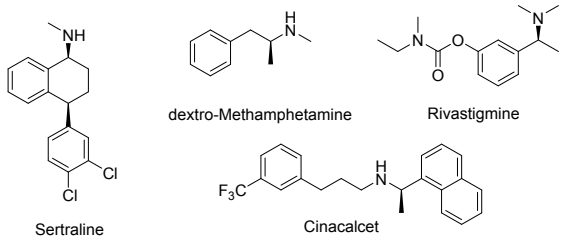
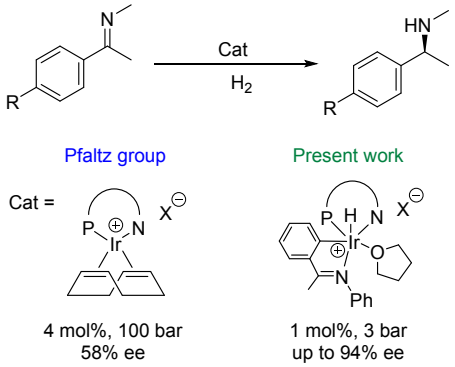


Figure 1: Chiral *N*-methyl and *N*-alkyl amine pharmaceuticals.

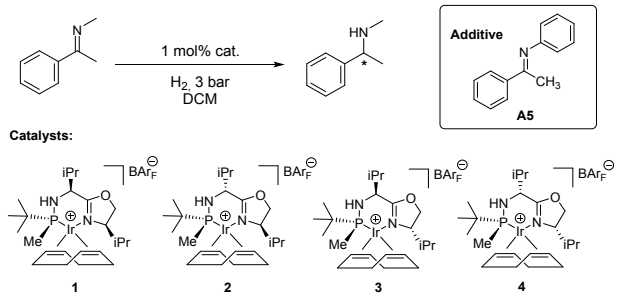
Scheme 1. Background vs. present work on the direct asymmetric hydrogenation of *N*-methyl imines.



We have recently reported that cationic Ir(I)-MaxPHOX catalysts are highly active and selective in the hydrogenation of *N*-aryl imines.[11,12] Here we tested whether these catalysts are also effective for *N*-methyl imine substrates (Table 1). The initial attempts to reduce the model *N*-methyl imine with four distinct diastereomers of Ir-MaxPHOX catalysts (**1-4)** were disappointing (Table 1, entries 1-4). A maximum enantiomeric excess of 71% was obtained with catalyst **2**, but with only 41% conversion. In 2013, Pfaltz and co-workers reported that the catalyst in the hydrogenation of *N*-aryl imines is an iridacycle that forms upon reaction with the imine substrate.[13] We have previously isolated and characterized cyclometallated [IrHCl(MaxPHOX)(imine)] complexes.[11] With this in mind, we hypothesized that, with the addition of the proper cyclometallating agent, a novel iridacycle would show an enhanced

capacity to reduce *N*-methyl imines. After testing a wide array of cyclometallating substances (**A1-A15**, see SI), we identified acetophenone *N*-phenyl imine (**A5**) as the best additive. Indeed, the addition 2 mol % of **A5** dramatically improved the reaction outcome with respect to both the conversion and selectivity (Table 1, entries 5-8). The best result was obtained with catalyst **1,** achieving an unprecedented 90% ee (Table 1, entry 5).

Table 1. Catalyst optimization.[a]

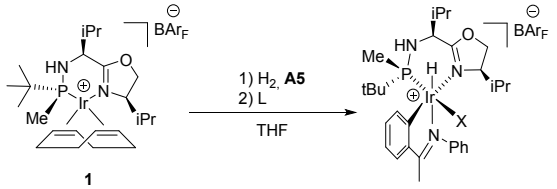


Entry	Cat.	Additive[a]	Conv. (%)[b]	ee (conf.)[c]
1	**1**	-	100	13(*R*)
2	**2**	-	41	71(*S*)
3	**3**	-	100	9(*R*)
4	**4**	-	6	11(*R*)
5	**1**	**A5**	100	90(*S*)
6	**2**	**A5**	100	61(*S*)
7	**3**	**A5**	100	78(*R*)
8	**4**	**A5**	36	86(*R*)

a) 2 mol% of additive was added prior to the addition of the imine substrate. b) Conversion was determined by ^{1}H NMR. c) Enantiomeric excess was determined by chiral HPLC analysis of the corresponding trifluoroacetate. Absolute configuration was determined by optical rotation of the free amine.

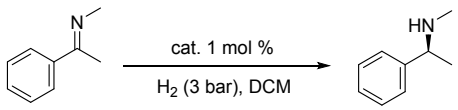
To achieve a reliable and robust method applicable in large- or even industrial-scale reactions, it would be desirable to isolate a catalyst that can be used directly in hydrogenation reactions. As mentioned above, neutral cyclometallated Ir(III)HCl complexes have been prepared and isolated; however, these complexes require activation by the addition of $NaBAr_F$.[11,13] We envisaged that an active precatalyst could be achieved if the reactive coordination site was stabilized with a transient ligand. To this end, complex **1** was reacted, in the presence of hydrogen, with acetophenone *N*-phenyl imine (**A5**), and the resulting complex was treated with several stabilizing ligands (Table 2). The use of CH_3CN, Ph_3P and Me_3P as ligands provided a single stereoisomer of the corresponding cationic octahedral Ir(III) complexes **5-7**, as shown by ^{1}H and ^{31}P NMR spectra. Pressurization with ethylene gas (3 bar) afforded complex **8**, also as a single stereoisomer. However, **8** did not contain an ethylene ligand but a solvent molecule instead (Table 2, entry 4). As expected, complex **8** could be synthesized without the addition of ethylene, interestingly, the resulting complex was of lower purity, as determined by ^{1}H NMR spectroscopy (see SI). We hypothesized that ethylene assists in the isomerization of intermediate unsaturated species to yield the final compound. To our delight, complexes **5-8** are stable solids that can be handled in air and stored under nitrogen (see SI for X-ray structure of **7**).

Table 2. Synthesis of Ir(III)H cyclometallated catalysts.



Entry	Added L	Yield (%)	X	Complex
1	CH_3CN	92	CH_3CN	**5**
2	Ph_3P	94	Ph_3P	**6**
3	Me_3P	96	Me_3P	**7**
4	Ethylene	98	THF	**8**

Table 3: Catalysis with cyclometallated Ir(III)H catalysts.



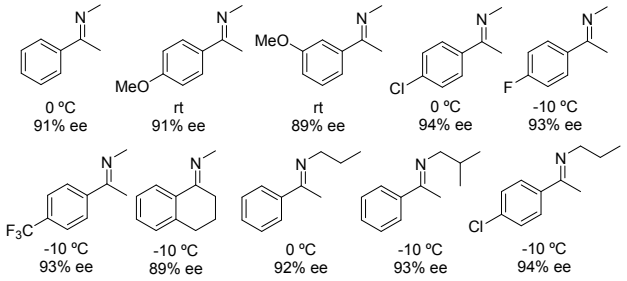
Entry	cat.	T (°C)	Conv. (%)[a]	ee (%)[b]
1	**5**	rt	100	85
2	**6**	rt	0	-
3	**7**	rt	100	90
4	**8**	rt	100	91
5	**7**	0	0	-
6	**8**	0	100	91

a) Conversion was determined by ^{1}H NMR. b) Enantiomeric excess was determined by chiral HPLC analysis of the corresponding trifluoroacetate.

Complexes **5-8** were used as catalytic precursors in the hydrogenation of acetophenone *N*-methyl imine (Table 3). We found that complexes containing CH_3CN (**5**), PMe_3 (**7**) and THF (**8**) provided 100% conversion at room temperature while the catalyst containing a PPh_3 (**6**) proved inactive (Table 3, entry 2). Catalysts **7** and **8** provided the best selectivity, 90 and 91% ee respectively, which parallels that achieved with the catalyst generated *in situ* (Table 3, entries 3 and 4). When the reaction temperature was lowered to 0 °C, complex **8** maintained its activity, while the Me_3P analog (**7**) was no longer active (Table 3, entries 5 and 6). We assumed that, in the presence of hydrogen, the solvent fragment in **8** is quickly released, thereby allowing faster activation.[14]

Using catalyst **8,** we next addressed the hydrogenation of several *N*-methyl and *N*-alkyl ketimines. The results are summarized in Figure 2. Full conversions were obtained in all cases. Reactions at low temperature (0–10°C) generally produced higher selectivity. Imines derived from 4- and 3-methoxyacetophenone were less reactive. In this regard, the hydrogenation had to be conducted at room temperature and the enantiomeric excesses for the corresponding amines were 91 and 89%, respectively. For the substrates containing electron-withdrawing groups (*p*-Cl, *p*-F and *p*-CF_3), the temperature was decreased to –10 °C, which improved selectivity, allowing up to 93-94% ee. *N*-Methyl imine derived from α-tetralone was hydrogenated, achieving 89% ee. Finally, excellent results were also obtained with imines derived from *N*-propyl and *N*-isobutyl amine. This observation thus indicates that *N*-alkyl imines can be hydrogenated with high selectivity (92-94% ee).[15]

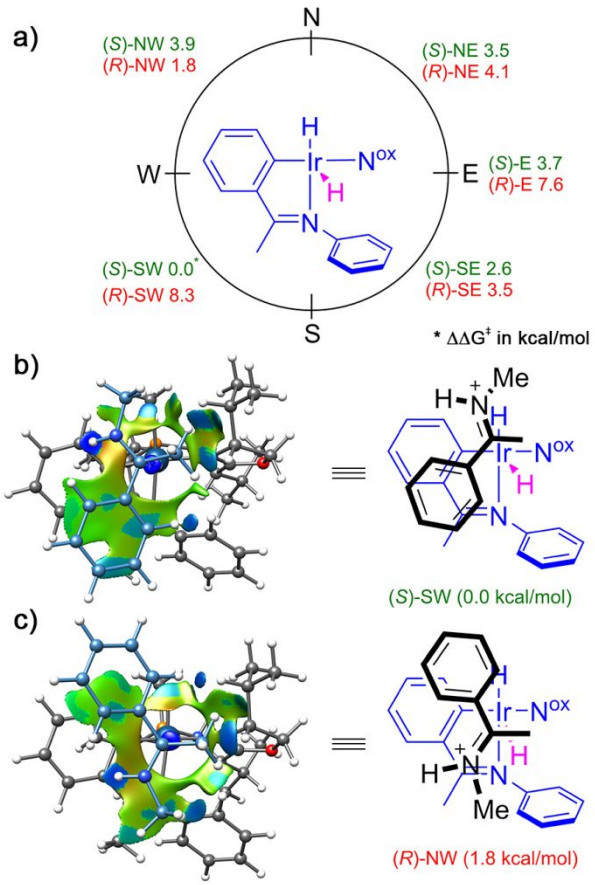
Figure 2: Results for the hydrogenation of *N*-methyl and *N*-alkyl imines using catalyst **8**.[a,b]



a) Hydrogenation reactions were run overnight in DCM at 3 bar of H_2 with 1 mol % of **8** at the temperature listed. 100% conversion was obtained in all cases, as determined by ^{1}H NMR. b) Enantiomeric excess was determined by chiral HPLC of the corresponding trifluoroacetamide.

The hydrogenation of *N*-phenyl imines has been proposed to proceed through an outer-sphere mechanism.[16] In order to understand the stereochemical course of the reaction a DFT mechanistic study using the B3LYP-D3 functional and including solvent effects has been performed in the present system (see SI for full details). The active catalyst is the iridium(III) hydride-dihydrogen complex that results from the ligand exchange of THF with H_2. The acidic dihydrogen complex protonates the imine-substrate and leads to an iminium ion which is not bound to the Ir center. The stereodetermining step is the intermolecular hydride-transfer from the resulting IrH_2 to the activated substrate. This is a lose TS in which multiple orientations of the substrate are possible. A quadrant model that accounts for the possible orientations of the iminium ion is depicted in Figure 3a. The most favorable TS is the one where the phenyl ring of the substrate is placed in the SW quadrant (Figure 3b) and leads to the *S* enantiomer as observed experimentally. The most favorable TS leading to the *R* isomer is 1.8 kcal mol^{-1} above with the phenyl group in the NW quadrant (Figure 3c). From these values the calculated enantiomeric excess is 90%, which is in close agreement with the experimental findings. Non-covalent interaction analysis[17] shows that in the (*S*)-SW TS the phenyl group of the iminium ion generates a larger π–π interaction surface than the (*R*)-NW TS (Figure 3b,c), thus leading to a more favorable transition sate. In support of this notion is the fact that the reduction of a purely aliphatic substrate like cyclohexylmethylketone *N*-methyl imine provided a racemate.[18]

Figure 3: a) DFT computed quadrant model for the hydride transfer stereodetermining step. Transition state relative ΔΔG‡ values for different orientations of the substrate phenyl group (in green: TSs leading to *S* isomer; in red: TSs leading to *R* isomer). The hydride transferred to the substrate is highlighted in magenta. b) Most favorable TS leading to *S* isomer, ΔΔG‡ = 0.0 kcal mol^{-1} (ΔG‡ = 6.3 kcal mol^{-1} with respect to the iminium intermediate). c) Most favorable TS leading to *R* isomer, ΔΔG‡ = 1.8 kcal mol^{-1}. Color code for NCI analysis: red: repulsive, blue: attractive.



In summary, we have described a novel cationic Ir(III)H catalyst that has allowed the first direct hydrogenation of methyl and alkyl imines in mild conditions and in high enantiomeric excess. The catalyst contains a *P*-stereogenic MaxPHOX ligand, a cyclometallated imine and a THF solvent molecule. The catalyst is a stable solid that can be stored under nitrogen. The THF ligand allows for fast and effective activation, even at reduced temperatures. DFT studies allowed to interpret the stereochemical course of the reaction. We think the findings reported herein contribute to advances in the development of hydrogenation iridium catalysts.

ASSOCIATED CONTENT

Supporting Information

Screening of additives data, experimental procedures, crystal data for **7**, NMR spectra for new compounds, and HPLC chromatograms. Crystallographic data in CIF format file for **7**. Computational methods and extended description of the computational results. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interests.

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(14) The integrity of the catalyst is preserved throughout the catalysis. GC analysis of the crude mixture after the reaction showed *N*-methyl imine substrate does not exchange with the cyclometallated *N*-phenyl imine. Moreover, the catalyst could be recovered after the reaction by trapping it with PMe_3. See supporting information for full details.

(15) The E/Z ratio of the starting imines as determined by ^{1}H NMR ranges between 95:5 and 100:0. We found no direct correlation between the E/Z ratio and the selectivity of the reaction. It is possible that the proposed iminium ion intermediate isomerizes under the reaction conditions.

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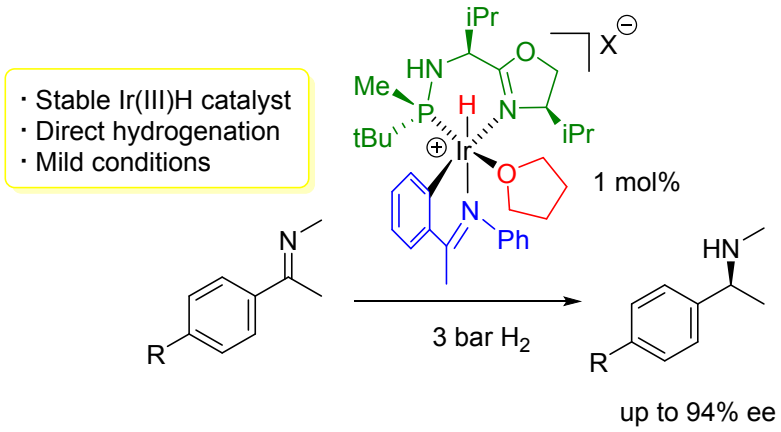
(18) Hydrogenation of cyclohexylmethylketone *N*-methylimine with 1 mol% of **8** provided a racemate with 50% conversion. Similar calculations to those reported in Figure 3 (quadrant model) for this substrate give a $\Delta\Delta G^{\ddagger}$ difference of only 0.1 kcal mol^{-1} between the most favorable TSs leading to opposite enantiomers. See supporting information for further details.

TOC Graphic


· Stable Ir(III)H catalyst
· Direct hydrogenation
· Mild conditions
iPr
HN
Me
P
H
N
O
iPr
tBu
Ir
X
1 mol%
N
Ph
O
N
R
3 bar H2
HN
R
up to 94% ee