Tetrahedron 74 (2018) 2182–2190

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

# A mechanistic investigation of an Iridium-catalyzed asymmetric hydrogenation of pyridinium salts

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ARTICLE INFO

*Article history:*
Received 13 January 2018
Received in revised form
10 March 2018
Accepted 13 March 2018
Available online 14 March 2018

*Keywords:*
Asymmetric hydrogenation
Iridium
Pyridinium salt
Chiral piperidine
Outer-sphere

ABSTRACT

NMR studies of the catalyst, deuteration experiments, mass spectrometry, and isolation and characterization of intermediates, allow us to propose an outer-sphere mechanism for the Iridium-catalyzed asymmetric hydrogenation of *N*-alkyl-2-arylpyridinium salts.



## 1. Introduction

The chiral piperidine core is ubiquitous in many natural products and is also a key pharmacophore in many medicinal agents.[1] Given the significance of this structural class, synthesis of these piperidines has attracted tremendous attention in academic and industrial laboratories.[2] From the perspective of atom economy, asymmetric hydrogenation of readily available substituted pyridines is the most direct and important approach to access chiral piperidines.[3]

A number of successful examples of pyridine reduction using either heterogeneous or homogeneous catalysts have been reported, including a variety of examples utilizing enantioselective Ir-catalyzed hydrogenation.[4] In 2014 we reported a highly enantioselective Ir-catalyzed asymmetric hydrogenation of simple *N*-benzylpyridinium salts using a unique phosphole MP$^2$-SEGPHOS as catalyst (Scheme 1).[5]

Over the past decades the mechanism of asymmetric hydrogenation of imine, alkene and N-heteroarenes has been investigated extensively.[6] In contrast, the mechanistic studies of Ir-catalyzed enantioselective hydrogenation of pyridine substrates have been scarce. In 2013, Xiao and co-workers reported an isotopic labeling experiment for the non-enantioselective, iodide anion promoted, rhodium-catalyzed transfer hydrogenation of N-benzylated pyridinium salts.[7a] In 2016, Lefort and co-worker reported the rhodium-catalyzed asymmetric hydrogenation of N-benzyl 3-substituted pyridinium salts.[7b] In this report, the authors elucidated the reaction pathway with deuterium labeling experiments. Soon afterwards Lefort and co-workers also reported the hydrogenation of 2-substituted pyridinium salts by iridium complexed to a mixture of ligands and identified an iminium intermediate prior to the final enantioselective reduction step.[7c] In the meanwhile, we also independently investigated the reaction mechanism of our previously reported enantioselective reduction of 2-aryl-pyridinium salts with the Ir-MP$^2$-SEGPHOS catalyst through a series of deuteration experiments. We then structurally characterized the catalyst by NMR and identified reaction intermediates to gain further mechanistic insight. Through these studies we propose a probable multi-step hydrogenation cascade that involves multiple tautomerizations followed by an enantioselective addition via an outer-sphere mechanism.

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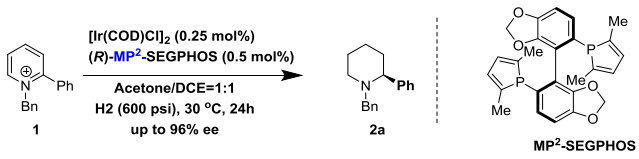
https://doi.org/10.1016/j.tet.2018.03.031
0040-4020/




**Scheme 1.** Ir/MP$^2$-SEGPHOS catalyzed hydrogenation of 2-phenyl-pyridinium salt.

## 2. Results and discussion

### 2.1. NMR studies of the catalyst

First, we studied the structure of the precatalyst by NMR. $[Ir(COD)Cl]_2$ and MP$^2$-SEGPHOS were mixed at the 1:2 M ratio in the solvent of acetone-$d_6$. The proposed structure is shown in Fig. 1.

The NMR data, shown in Fig. 2, support a structure with pseudo $C_2$ symmetry. Specifically, the protons and carbons on equivalent positions of MP$^2$-SEGPHOS and the COD moiety exhibited identical NMR chemical shifts (Fig. 2a). Interestingly, the $^{31}$P NMR spectrum, revealed broad (~130 Hz linewidth) but distinct resonances (9.3 ppm and 4.8 ppm) for the two phosphorus atoms on MP$^2$-SEGPHOS(Fig. 2b), revealing that this complex lacks rigorous symmetry Therefore, we propose that a $Cl^-$ counter-ion binds $Ir^+$ to make a charge-neutral complex and by doing so, it breaks $C_2$ symmetry. The *J* coupling between the two $^{31}$P atoms was not observed, presumably due to the small $^2J_{PP}$ cis coupling of less than 30 Hz in magnitude[8] and broad lines of ~130 Hz. Proton-phosphorus *J* correlations were observed for both MP2-SEGPHOS and COD in the $^1$H-$^{31}$P HMBC experiment (Fig. 2c), and intermolecular NOEs were observed between MP$^2$-SEGPHOSand COD (dash circled in Fig. 2d), suggesting the formation of an Ir(COD) (MP$^2$-SEGPHOS) complex.

The activated catalyst was obtained by applying 600 psi $H_2$ pressure to the precatalysts for 16 h. Due to apparent instability of the complex, the potential stabilizing effects of various counter-ions were also evaluated. It was found that including 2.5 fold molar equivalents of $NH_4Br$ provided appreciable stabilization, although significant decomposition still occurred after 20 h, as indicated by decaying hydride.

NMR signal intensities. As shown in Fig. 3, the resulting activated catalyst lacks a single major constituent but instead contains a complex mixture of different species and possibly stereoisomers. Based on $^1$H chemical shift distribution and differential effects of $^{31}$P-decoupling on $^1$H resonances, we classified the hydride spectrum into four regions labeled as “a”, “b”, “c”, and “d” in Fig. 3a. Region “a” contains four major peaks with a “doublet of doublet” $^{31}$P coupling pattern. The primary and secondary couplings are ca. 150 Hz and 17 Hz, which are consistent with “trans” and “cis” couplings to the two different phosphorus atoms on MP$^2$-SEGPHOS, respectively. Therefore, hydrides in region “a” should be in the coordination plane with MP$^2$-SEGPHOS. Region “b” includes a number of hydride signals lack apparent coupling to $^{31}$P, as $^{31}$P-decoupling has minimal effects on their $^1$H line-shapes. Therefore, these hydrides unlikely reside on the catalytic complex of interest. Region “c” contains a number of broad signals that are substantially sharpened upon $^{31}$P-decoupling. The observation suggested these hydrides have small couplings with more than one $^{31}$P atoms, but the exact coupling constants could not be reliably extracted due to linewidth. Region “d” contains two sharp triplet peaks, which arise from hydrides that are coupled to two $^{31}$P atoms through constants of 14–18 Hz. The hydrides in “d” bind Iridium perpendicularly to the MP$^2$-SEGPHOS ligand plane and thereby have small “cis” couplings to both phosphorus atoms.

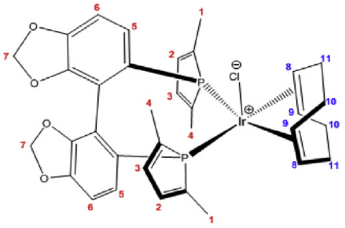


**Fig. 1.** Proposed structure of Ir(COD) (MP$^2$-SEGPHOS) precatalyst. Protons of identical chemical shifts are indicated by the same numbers.

The NOESY experiment further suggests that hydrides in regions “a” and “c” form a di-hydride complex, as shown in Fig. 4. As mentioned earlier, region “a” hydrides are co-planar with MP$^2$-SEGPHOS with both a large and a small $^{31}$P coupling, so region “c” hydrides, which bear two small $^{31}$P couplings, should bind perpendicularly to MP$^2$-SegPhos. This disposition also places the two hydrides in proximity, which can readily lead to NOE signals, as observed in Fig. 3d. The chemical shifts of regions “a” and “c” around −12 ppm and −22pm, and the large “trans” and small “cis” $^1$H-$^{31}$P couplings of 150 and 17 Hz, are consistent with values reported for a different Ir-diphosphine-dihydride complex of a similar coordination geometry.[9] The “$X_1$” position is occupied by a counter-ion ($Br^-$ or $Cl^-$), whereas the “$X_2$” position is occupied by a solvent molecule. Note that “$X_1$” is unlikely occupied by a solvent, because a hydride on the anti-position of a solvent generally has a chemical shift of ca. −30 ppm or even more upfield,[10] whereas the “c” hydrides display chemical shifts of −22 ppm. The presence of several distinct di-hydride species, as indicated by multiple signals in each region, may arise from different stereoisomers and/or from binding of different counter-ions. The formation of oligomeric Ir-complexes may also contribute to the observed spectral heterogeneity.[8d,10c] Note that Fig. 4 only shows only one possible stereoisomer. A different stereoisomer, which arises by swapping the positions of the “a” hydride with “$X_1$”, is also consistent with both $^1$H-$^{31}$P couplings and NOESY data. This stereoisomer and the one displayed in Fig. 4 are diastereomers, because MP$^2$-SEGPHOS is atropchiral. Hydrides in Region “b”, which are not part of the catalytic complex of interest, in fact undergo exchange at the ms-s time scale with hydrides “a”, as seen by exchange peaks of negative correlation in NOESY spectrum, which also shows indirect NOESY correlations to hydrides “c”. The chemistry relevance of this hydride pool is not clear to us. For the two hydrides in region “d”, lack of NOESY cross peaks supports that they likely belong to two different mono-hydride species. They unlikely reside on a single di-hydride species with two “trans” disposed protons, due to unequal peak integrals. We cannot rule out the possibility that they are from two different di-hydride species both with two equivalent protons of “trans” configuration, but $^1$H-$^{31}$P HMBC shows two distinct $^{31}$P signals coupled to each hydride (data not shown), which indicates the corresponding complex lacks rigorous symmetry.

### 2.2. Deuteration experiments

Although the pyridine 2-phenyl position is known to undergo asymmetric hydrogenation as described earlier, the reaction symmetry on other pyridine positions is unknown due to a lack of chirality on those positions in the final product. However, one can actually introduce chirality into these positions by reducing pyridine with deuterium gas, and by determining the configuration of these –CHD centers to gain mechanistic insight into the hydrogenation process. In the deuteration experiment, *N*-benzyl-2-phenylpyridinium bromide **1** was exposed to 99.9% $D_2$ and upon reaction completion the crude was subjected to NMR analysis for