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A Mixed Ligand Approach for the Asymmetric Hydrogenation of 2-Substituted Pyridinium Salts

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Abstract: Herein we describe a new methodology for the asymmetric hydrogenation (AH) of 2-substituted pyridinium salts. An iridium catalyst based on a mixture of a chiral monodentate phosphoramidite and an achiral phosphine was shown to hydrogenate *N*-benzyl-2-arylpyiridinium bromides to the corresponding *N*-benzyl-2-arylpiperidines with full conversion and good enantioselectivity. The mechanism of the reaction under optimized conditions was investigated *via* kinetic measurements and isotopic labeling experiments. Our study suggests that the hydrogenation starts with a 1,4-hydride addition and that the enantiodiscriminating step involves the reduction of an iminium intermediate.

Keywords: asymmetric catalysis; homogeneous catalysis; hydrogenation; pyridines; reaction mechanisms

The asymmetric hydrogenation (AH) of substituted N-heteroarenes is an attractive route towards chiral cyclic amines that are ubiquitous motifs in nature and in active pharmaceutical ingredients.[1] Among N-heteroarenes, 2- and 3-substituted pyridines are probably the most challenging AH substrates. Their six-membered ring has indeed an aromatic resonance energy close to that of benzene,[2] and their reduction to piperidines requires the hydrogenation of three different double bonds. In addition, pyridines and piperidines can deactivate the catalyst *via* strong coordination to the metal center. Finally, these substrates also lack secondary coordinating groups that can contribute to improving the enantioselectivity.

A successful strategy in the AH of pyridines has been quaternization of the substrate.[3] Although some AHs of non-quaternized pyridines have been reported for very specific substrates,[4] most of the work involves pyridinium salts based on ylide formation,[5] *N*-benzylation[6] or protonation.[7] In some cases, a secondary coordinating group introduced during the quaternization appeared to be crucial to obtain high enantioselectivities.[6a]

In 2000, chiral monodentate phosphorus ligands were rediscovered and appeared to be as efficient as bidentate ligands in AH.[8] Since the active AH catalytic species based on bidentate phosphines contained 2 phosphorus atoms per metal center, the use of monodentate ligands led to the development of the so-called mixed ligand strategy.[9] Pioneered by the group of Reetz and us, this approach consists of performing the hydrogenation with a catalyst formed *in situ* from a metal precursor and a mixture of 2 different monodentate ligands with at least one of them being chiral. In the reaction mixture, a catalytic species containing both ligands (mixed ligand catalyst) is formed and in some cases exhibits improved performances compared to the corresponding single ligand species.[9] Here we report the application of the mixed ligand strategy in the AH of 2-substituted *N*-benzylated pyridinium salts using a catalyst formed *in situ* from $[Ir(cod)Cl]_2$, a chiral phosphoramidite[10] and an achiral phosphine. While the mechanism of the AH of N-heteroarenes has been extensively studied,[11] we noticed that mechanistic studies dealing with pyridine substrates were scarce.[12] Therefore we performed a range of experiments to uncover the mode of action of our most efficient mixed ligand catalyst.

N-Benzyl-2-phenylpyiridinium bromide (**1a**), prepared by reaction of 2-phenylpyridine with benzyl bromide, was chosen as model substrate. $[Ir(cod)Cl]_2$

was selected as metal precursor. An initial screening of 24 different monodentate chiral phosphoramidites was performed using high-throughput experimentation (see the Supporting Information). Three BINOL-based phosphoramidites were selected as starting point for a mixed ligand approach: PipPhos (**PA1**, entry 1) which gave the highest *ee* at full conversion, and **PA2**/**PA3** (Table 1, entries 2 and 3) which were identified as the most enantioselective ligands, albeit with uncomplete conversion.

All combinations between the three most enantioselective phosphoramidites **PA1–3** and 13 different achiral phosphines and phosphites (see the Supporting Information) were tested with $[Ir(cod)Cl]_2$ as the metal precursor. Considering that the phosphine is a stronger donor ligand than the phosphoramidite, a phosphoramidite:phosphine ratio of 2:1 was used to promote the formation of the mixed ligand catalyst. Gratifyingly, some improvements in terms of activity and enantioselectivity were obtained upon addition of aromatic phosphines (entries 4–12). The triphenylphosphine bearing trifluoromethyl groups in the *para*-position led to the best enantioselectivities (entries 11 and 12). Remarkably, the three phosphoramidites **PA1–3** were differently affected by combination with the same achiral phosphine (entries 4–6): no significant change was observed when **PA1** was combined with PPh_3 (entry 1 *vs.* 4). With **PA2**, the addition of PPh_3 improved the activity without affecting the enantioselectivity (entry 2 *vs.* 5). On the contrary, the addition of PPh_3 to **PA3** improved the enantioselectivity without affecting the yield (entry 3 *vs.* 6).

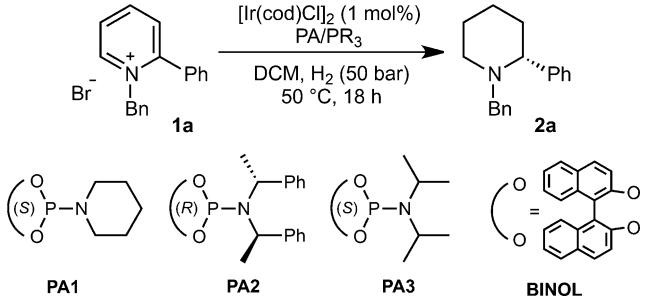
The ratio between iridium and the two ligands was investigated with **PA3** and $P(p\text{-}CF_3C_6H_4)_3$. For the phosphoramidite ligand alone, the optimal amount was 2 equivalents per iridium (entries 3, 13 and 14). A larger excess of **PA3** led to lower yields and enantioselectivities (entry 14). Remarkably, the achiral phosphine used alone led to no conversion (entries 15 and 16). Since the Ir-phosphine complex appeared to be inactive, we investigated lower phosphoramidite:phosphine ratios. The optimal iridium:**PA3**:phosphine ratio was determined to be 1:1:1 (entry 17), leading to full conversion to **2a** and 77% *ee*. An excess of phosphine or phosphoramidite (entries 12–18) led to a decrease in activity, probably due to the saturation of the metal complex by the extra ligand. In agreement with the lack of activity of the phosphine homo-complex, an excess of phosphine did not affect the enantioselectivity (entry 18). On the other hand, an excess of phosphoramidite led to a lower *ee* (entry 12) which is also consistent with the Ir complex containing two phosphoramidites being less enantioselective.

An extensive screening of solvents and additives did not result in an improved catalytic performance of the Ir/**PA3**/$P(p\text{-}CF_3C_6H_4)_3$ system. Decreasing the pressure of H_2 led to a lower conversion without affecting the enantioselectivity. Decreasing the temperature improved the *ee* to 83% but at the expense of the conversion (see the Supporting Information).

The substrate scope was investigated to some extent with the optimized system (Table 2). Indeed, the mixed ligand catalyst was efficient for a range of 2-arylpyridinium salts. Yields and enantioselectivities were very similar for these substrates, i.e., not drastically influenced by the electronic properties of the aryl substituent (Table 2, entries 1–6). Increasing the steric bulk of the aryl substituent led to a decrease of the enantioselectivity (Table 2, entry 7).

A mechanistic study was performed with the optimized catalyst. The AH of pyridinium salt **1a** was monitored over time by GC and NMR (Figure 1). The substrate was fully consumed in roughly 10 h, with concomitant formation of piperidine **2a**, whose

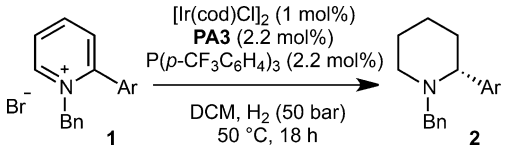
Table 1. Selected results for the ligand screening in the AH of **1a** to **2a**.[a]



Entry	**PA** [equiv./Ir][b]	PR_3, R = [equiv./Ir][b]	Yield [%][c]	*ee* [%][c]
1	**PA1** [2]	–	99	30
2	**PA2** [2]	–	49	−52
3	**PA3** [2]	–	86	39
4	**PA1** [2]	Ph [1]	94	31
5	**PA2** [2]	Ph [1]	87	−49
6	**PA3** [2]	Ph [1]	88	50
7	**PA2** [2]	*p*-$MeOC_6H_4$ [1]	88	−56
8	**PA3** [2]	*p*-$MeOC_6H_4$ [1]	86	55
9	**PA2** [2]	*p*-ClC_6H_4 [1]	51	−54
10	**PA3** [2]	*p*-ClC_6H_4 [1]	47	56
11	**PA2** [2]	*p*-$CF_3C_6H_4$ [1]	83	−58
12	**PA3** [2]	*p*-$CF_3C_6H_4$ [1]	86	60
13	**PA3** [1]	–	60	17
14	**PA3** [4]	–	31	2
15	–	*p*-$CF_3C_6H_4$ [1]	3	–
16	–	*p*-$CF_3C_6H_4$ [2]	2	–
17	**PA3** [1]	*p*-$CF_3C_6H_4$ [1]	99	77
18	**PA3** [1]	*p*-$CF_3C_6H_4$ [2]	71	77

[a] *Reaction conditions*: **1a** (0.05 mmol), $[Ir(cod)Cl]_2$ (1 mol%), phosphoramidite (**PA**), phosphine (PR_3), DCM (1 mL), 50 °C, 50 bar H_2, 18 h.
[b] Equivalents of ligand per atom of iridium.
[c] Determined by chiral GC analysis and dodecane as internal standard. Positive values correspond to *R* configuration.

Table 2. Substrate screening for AH of *N*-benzyl-2-arylpyridinium salts.[a]



Entry	Ar	Yield [%][b]	*ee* [%][b]
1	Ph (**1a**)	99 (92)[c]	77 (*R*)
2	4-MeC_6H_4 (**1b**)	98	71 (+)
3	4-$MeOC_6H_4$ (**1c**)	99	82 (+)
4	3,5-di-$MeOC_6H_3$ (**1d**)	97	70 (+)
5	4-$CF_3C_6H_4$ (**1e**)	98	74 (+)
6	4-ClC_6H_4 (**1f**)	99	74 (+)
7	2-naphthyl (**1g**)	99	58 (−)

[a] *Reaction conditions*: **1** (0.1 mmol), $[Ir(cod)Cl]_2$ (1 mol%), **PA3** (2.2 mol%), $P(p\text{-}CF_3C_6H_4)_3$ (2.2 mol%), DCM (2 mL), 50 °C, 50 bar H_2, 18 h.

[b] Yield and *ee* determined by chiral GC, HPLC or SFC with dodecane as internal standard.

[c] In brackets, isolated yield of a 500-mg-scale reaction.

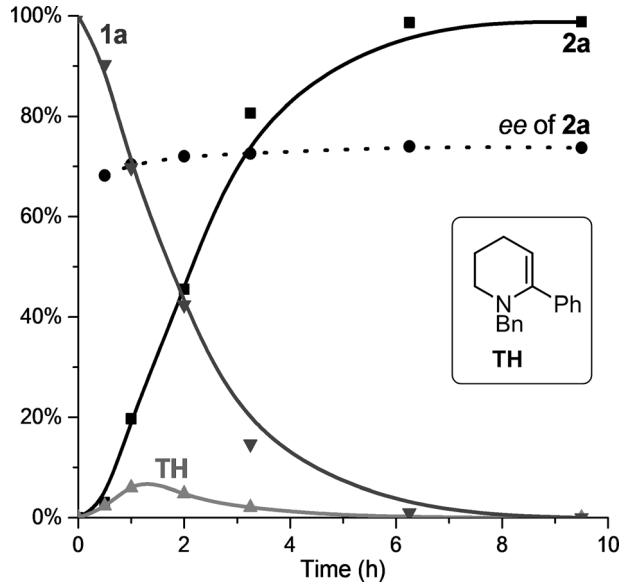


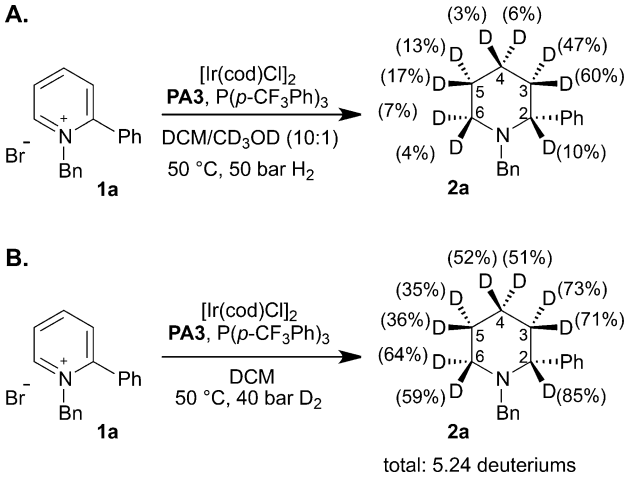
Figure 1. Evolution of the yield and *ee* of different reaction species over time. *Reaction conditions*: **1a** (1.5 mmol), $[Ir(cod)Cl]_2$ (1 mol%), **PA3** (2.2 mol%), $P(p\text{-}CF_3C_6H_4)_3$ (2.2 mol%), DCM (30 mL), 50 °C, 50 bar H_2, 10 h. Consumption of **1a** determined by NMR with dimethyl terephthalate as internal standard. Yield and *ee* of **2a** and **TH** monitored by chiral GC analysis with dodecane as internal standard.

ee increased slightly at the beginning of the reaction and then remained constant. The reaction profile fits well with a 1st order reaction, with a small induction period during the first minutes.

A reaction intermediate (labeled **TH** in Figure 1) was detected by GC. Its concentration reaches a maximum after 1.5 h. Although it could not be isolated, its mass ($m/z = 249$) determined by GC-MS was consistent with an *N*-benzylated tetrahydropyridine isomer. NMR analysis allowed us to identify **TH** as *N*-benzyl-6-phenyl-1,2,3,4-tetrahydropyridine (Figure 1, see the Supporting Information). During the course of the reaction, the sum of **1a**, **2a** and **TH** matched well with the initial amount of substrate used, suggesting that no other intermediates are formed and that the hydrogenation of **TH** is the rate-limiting step.

To get further insight into the mechanism, two isotopic labeling experiments were conducted (Scheme 1). When the optimized reaction was carried out with H_2 in the presence of CD_3OD (Scheme 1A), a high deuterium incorporation was observed at C-3 (1.07 deuteriums) and C-5 (0.30 deuteriums), compared to the other carbons (< 0.12 deuteriums each). This suggests that enamine-iminium tautomerizations take place during the reaction leading to the addition of a proton from the reaction medium into the positions 3 and 5 in agreement with previous studies for other N-heteroaromatic substrates.[11]

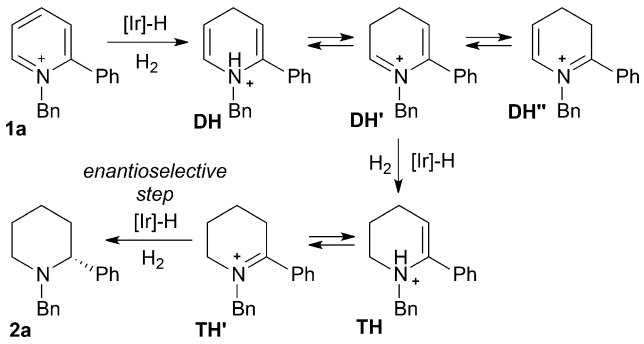
The low deuterium incorporation at C-4 is consistent with an initial 1,4-hydride addition to **1a** leading to the formation of *N*-benzyl-2-phenyl-1,4-dihydropyridine (**DH**, Scheme 2). The dihydropyridine **DH** can tautomerize into the two iminium ions **DH′** and **DH″**. Since **TH** is the only detectable intermediate, it is reasonable to think that the 1,2-hydride addition to **DH′** occurs faster than to the more sterically hindered **DH″**. The difference of reactivity between **DH′** and **DH″** is also consistent with the higher deuterium incorporation at C-3 compared to C-5. Since **DH″** is a more stable intermediate, it can incorporate more deuterium at C-3 *via* multiple enamine-iminium interconversions.



Scheme 1. Isotopic labeling experiment for the AH of *N*-benzyl-2-phenylpyridinium bromide **1a** in the presence of CD_3OD (**A**) or D_2 (**B**).

A second isotopic labeling experiment was performed by reacting **1a** with D_2 gas under the optimized conditions (Scheme 1B): all the ring positions were deuterated, with a total amount of five deuterium atoms incorporated. No ring-face preference for the deuterium incorporation is observed in any of the carbons suggesting that the stereogenic center is not formed until the last step.

Based on these experimental results, the following mechanism can be proposed (Scheme 2): an initial 1,4-hydride addition to **1a**, forming the dihydropyridine **DH**; the rapid hydrogenation of **DH** into **TH** *via* an iminium intermediate **DH′**; the enantioselective 1,2-hydride addition to the iminium **TH′** to the final piperidine **2a**.



Scheme 2. Proposed mechanism for the asymmetric hydrogenation of **1a**.

In conclusion, we have developed a new catalytic system based on a mixture of ligands for the asymmetric hydrogenation of 2-arylpyridines. Using an iridium complex in the presence of two different monodentate ligands (a chiral phosphoramidite and an achiral phosphine), full conversions and *ee*s up to 82% were obtained. A mechanistic study was performed and allowed us to propose **DH** and **TH** as the intermediates in the hydrogenation of **1a** to **2a**. The mixed ligand strategy is attractive since a large number of catalytic systems can be generated through the simple combination of monodentate ligands. Therefore we anticipate that *via* high-throughput screening, novel mixed ligands catalysts for the hydrogenation of related substrates will soon be discovered.

Experimental Section

General Procedure

Inside the N_2 glovebox, a solution of $[Ir(cod)Cl]_2$ (0.0015 mmol), **PA3** (0.0033 mmol) and $P(p\text{-}CF_3C_6H_4)_3$ (0.0033 mmol) in DCM (1 mL) was stirred at 45 °C for 30 min. The preformed catalyst was added to a 5-mL-vial containing a solution of the corresponding *N*-benzyl-2-arylpyridinium bromide (0.15 mmol) in DCM (2 mL). The vial was capped with a PTFE septum, removed from the glovebox and placed into a Premex 96er Multireaktor. After flushing it 5 times with N_2 (10 bar) and 5 times with H_2 (10 bar), it was pressurized to 50 bar of H_2 and the mixture stirred at 50 °C for 18 h. The crude mixture was washed with a saturated aqueous solution of Na_2CO_3 and extracted with DCM. The organic extracts were dried, concentrated and purified by flash column chromatography using hexane/EtOAc (from 99:1 to 95:5).

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