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Iridium-Catalyzed Selective Hydrogenation of 3-Hydroxypyridinium Salts: A Facile Synthesis of Piperidin-3-ones

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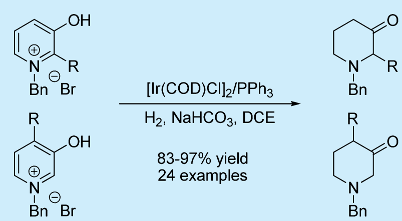
S Supporting Information

ABSTRACT: The selective hydrogenation of 3-hydroxypyridinium salts has been achieved using a homogeneous iridium catalyst, providing a direct access to 2- and 4-substituted piperidin-3-one derivatives with high yields, which are important organic synthetic intermediates and the prevalent structural motifs in pharmaceutical agents. Mild reaction conditions, high chemoselectivity, and easy scalability make this reaction highly practical for the synthesis of piperidin-3-ones.



The piperidin-3-one is an important and versatile intermediate for the synthesis of diverse natural products and pharmaceutical agents. For example, the 2- or 4-substituted piperidin-3-one could be easily hydrogenated to chiral piperidin-3-ol using Noyori's ruthenium catalyst through dynamic kinetic resolution.[1] The optically active piperidin-3-ol serves as core structure in naturally occurring alkaloids Febrifugine,[2] Swainsonine,[3] and bioactive molecules such as human NK1 receptor antagonist L-733,060[4] and human renin inhibitor[5] (Figure 1).

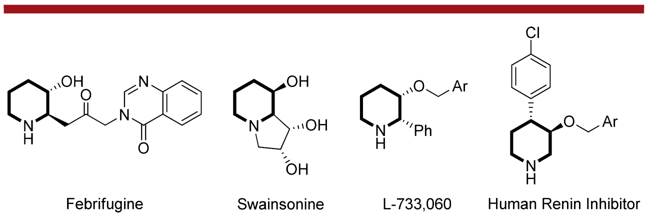
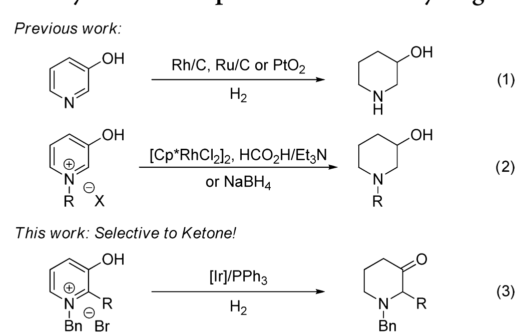


Figure 1. Selected natural products and pharmaceutical agents containing chiral piperidin-3-ol motifs.

Through reductive amination, piperidin-3-one could be transformed to piperidin-3-amine,[6] which is also the core framework for pharmaceutical agents such as CP-99,994.[7] Despite their importance, methods for the efficient preparation of piperidin-3-one remain scarce and often require additional preparatory steps from the starting material.[8] Thus, the development of a synthetic, step-effective, and scalable method method for the piperidin-3-one is highly desirable.

As the aromatic pyridin-3-ols are easily available and abundant, selective hydrogenation of these substrates to ketones would represent a straightforward, practical, and step-economical approach to piperidin-3-ones. Although the hydrogenation of aromatic compounds has made great progress in the past decades,[9] pyridine rings still lag behind.[10,11] Selectively reducing pyridinol to the corresponding ketone encounters several challenges. First, the high aromatic stability of the pyridine ring must be overcome for the efficient hydrogenation. Second, both the pyridinol and the hydrogenated product possess strong coordination ability which easily causes the deactivation of the catalyst. Third, because of the high reactivity of piperidinone, it is difficult to avoid its deep hydrogenation to piperidinol under the reaction conditions. Represented by Han and Jiang's finding of a dual-supported Pd/C Lewis acid catalyst, the selective hydrogenation of phenol to cyclohexanone has made significant progress.[12] In contrast, there are hardly any reports on the selective hydrogenation of pyridinol to piperidinone (Scheme 1).

Scheme 1. Synthesis of Piperidin-3-one via Hydrogenation



The direct hydrogenation of pyridine-3-ol with heterogeneous catalyst Rh/C, Ru/C, or PtO_2 generally delivered piperidin-3-ol as the sole product (eq 1).[13] Pyridine could be transformed to a *N*-alkyl-pyridinium salt, which possesses higher activity than the corresponding pyridine. Unfortunately, the reduction of such a salt of pyridine-3-ol employing either a rhodium catalyst or

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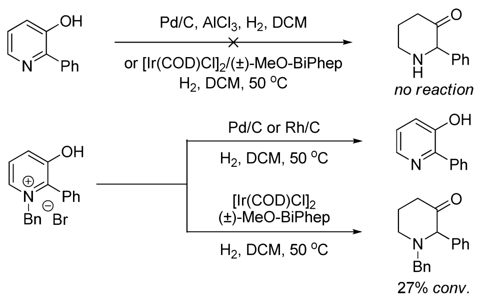
stoichiometric metal hydride reagents delivered exclusively a piperidin-3-ol product.[14] In connection with our program exploring the application of a substrate activation strategy in the hydrogenation of aromatics[15] and considering that the iminium salt exhibited higher activity than the ketone in hydrogenation, we envisaged that selective hydrogenation of the 3-hydroxypyridinium salt to ketone could be realized through careful optimization of the reaction conditions. Herein, we report a scarce homogeneous iridium-catalyzed selective hydrogenation of 3-hydroxypyridinium salts to piperidin-3-one derivatives with high yield and chemoselectivity (eq 3, Scheme 1).

We began our exploration with 2-phenylpyridin-3-ol as the model substrate (Scheme 2). An initial screening of the catalyst

Scheme 2. Initial Catalyst Screening

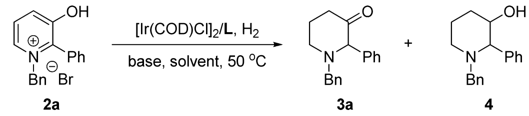


was performed. It was found that Han's Pd/C-$AlCl_3$ catalyst system was completely ineffective with this substrate. Neither piperidin-3-one nor piperidin-3-ol product could be detected after the hydrogenation. The homogeneous iridium catalyst delivered the same result. These facts reflected that the hydrogenation of pyridin-3-ol was a more difficult task.

Recently, our group has reported the successful asymmetric hydrogenation of *N*-benzylpyridinium salts which were readily formed upon reaction with benzyl bromide.[10c] Since the aromaticity of the pyridine ring is partially destroyed, these salts possess much higher activity than the corresponding pyridines. So, we decided to apply this strategy to the hydrogenation of pyridin-3-ol. First, different catalysts were screened again. The results were disappointing with the heterogeneous catalyst such as Pd/C or Rh/C, only delivering the debenzylated product, which might be ascribed to their preference to cleave the C−N bond. Pleasingly, the homogeneous iridium catalyst was promising, selectively giving piperidin-3-one as the only detectable product, albeit the conversion was low.

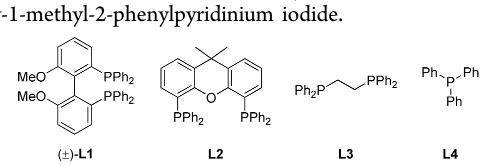
Encouraged by these preliminary results, we made further efforts to optimize the reaction conditions to increase catalyst activity (Table 1). Following our previous work,[15b] an inorganic base was added to the reaction system, and the conversion was greatly increased. However, a certain amount of piperidin-3-ol product emerged, and the ratio of ketone to alcohol was 8:1 (entry 2). Solvent screening showed that DCE was the best choice, giving a full conversion and a slightly higher selectivity (entry 6). To further increase the selectivity, a variety of inorganic and organic bases were screened, but none gave a better result than the initially used sodium bicarbonate (entries 7−9). Considering that the selectivity of the catalyst was greatly influenced by the ligand, we turned our attention to the screening of the ligands. To our surprise, the simple triphenylphosphine turned out to be the best choice, giving full conversion and perfect selectivity (entry 12). The current catalyst system was a

Table 1. Evaluation of Reaction Parameters[a]



entry	solvent	ligand	base	conv (%)[b]	3a:4[b]
1	DCM	**L1**	–	27	>20:1
2	DCM	**L1**	$NaHCO_3$	72	8:1
3	THF	**L1**	$NaHCO_3$	>95	2:1
4	EtOAc	**L1**	$NaHCO_3$	>95	2:1
5	$CHCl_3$	**L1**	$NaHCO_3$	53	7:1
6	DCE	**L1**	$NaHCO_3$	>95	11:1
7	DCE	**L1**	Na_2CO_3	76	11:1
8	DCE	**L1**	K_3PO_4	87	10:1
9	DCE	**L1**	DIPEA	79	5:1
10	DCE	**L2**	$NaHCO_3$	>95	10:1
11	DCE	**L3**	$NaHCO_3$	>95	2:1
12	DCE	**L4**	$NaHCO_3$	>95	>20:1
13[c]	DCE	**L4**	$NaHCO_3$	83	>20:1
14[d]	DCE	**L4**	$NaHCO_3$	>95	17:1
15[e,f]	DCE	**L4**	$NaHCO_3$	>95 (93)	>20:1
16[d,g]	DCE	**L4**	$NaHCO_3$	>95 (84)	>20:1

[a]Conditions: **2a** (0.20 mmol), $[Ir(COD)Cl]_2$ (1.0 mol %), **L** (2.2 mol %); for **L4** (4.4 mol %), H_2 (600 psi), base (0.2 mmol), for Na_2CO_3 and K_3PO_4 (0.1 mmol), solvent (3.0 mL), 50 °C, 20 h; DIPEA = *N*,*N*-diisopropylethylamine. [b]Determined by ^1H NMR; **4** was a mixture of two diastereomers. [c]40 °C. [d]60 °C. [e]$[Ir(COD)Cl]_2$ (0.5 mol %), **L4** (2.2 mol %). [f]93% was the isolated yield. [g]The substrate was 3-hydroxy-1-methyl-2-phenylpyridinium iodide.



little sensitive to temperature; decreasing or increasing the temperature led to slightly inferior results (entries 13−14). Notably, decreasing the catalyst loading to 1.0 mol % had no negative effects, and a 93% isolated yield was still obtained (entry 15). Other *N*-alkyl-substituted substrates such as 3-hydroxy-1-methyl-2-phenylpyridinium iodide were also suitable, affording the corresponding ketone in 84% yield (entry 16).

With the optimized reaction conditions established, the substrate scope of the iridium-catalyzed selective hydrogenation of 3-hydroxypyridinium salts was explored (Figure 2). In general, all the substrates performed very well under the standard conditions. Initially, substrates with various electron-donating groups were examined, and good to excellent yields were obtained (**3b**−**g**). However, presumably owing to the steric hindrance, the substrate **2b** containing a methyl group at the *ortho* position of the phenyl ring needed a higher catalyst loading. Substrates halogenated at different positions had little influence on the activity (**3h**−**k**). Other electron-withdrawing groups such as ester and trifluoromethyl were also tolerant, affording the corresponding piperidin-3-ones in excellent yields (**3l**−**m**). For the naphthyl substituted **3n**, a slightly lower yield was obtained. 2-Alkyl substituted substrates were suitable substrates, but less active than the corresponding 2-aryl substituted ones, so a higher reaction temperature was needed to reach full conversion (**3o**−**p**).

Next, the simple 1-benzyl-3-hydroxypyridinium bromide **2q** with a hydrogen at the 2-position was also subjected to the standard conditions, and the piperidin-3-one **3q** could be

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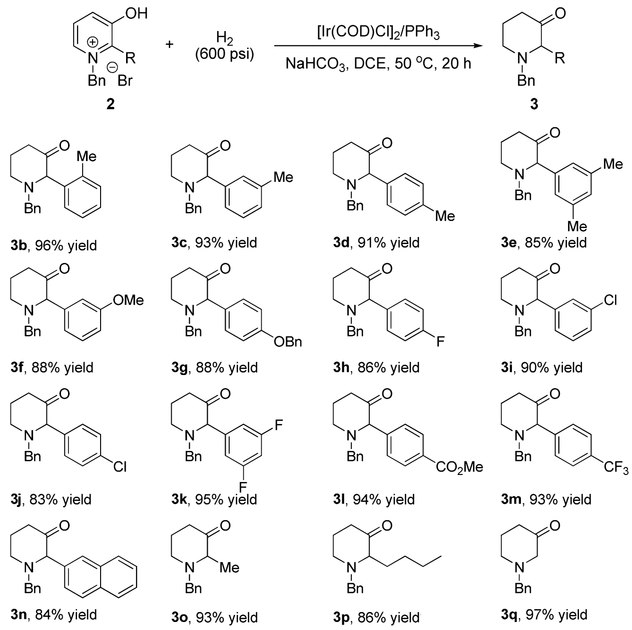
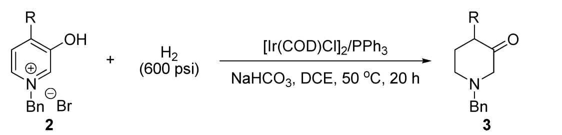


Figure 2. Substrate scope for the 2-substituted 3-hydroxypyridinium salts. Conditions: **2** (0.20 mmol), $[Ir(COD)Cl]_2$ (0.5 mol %), PPh_3 (2.2 mol %), H_2 (600 psi), $NaHCO_3$ (0.20 mmol), DCE (3.0 mL), 50 °C, 20 h. Isolated yields are provided. For **3b**, $[Ir(COD)Cl]_2$ (1.0 mol %) and PPh_3 (4.4 mol %) were used. For **3o** and **3p**, the reaction temperature was 60 °C.

obtained in almost quantitative yield. This demonstrated that the high chemoselectivity to afford the ketone in the current system was not governed by the steric effect of the 2-position.

We next explored the substrate scope of 4-substituted 3-hydroxypyridinium salts, and the results are summarized in Table 2. Various 4-aryl-piperidin-3-ones were readily accessed with

Table 2. Substrate Scope for the 4-Substituted 3-Hydroxypyridinium Salts[a]



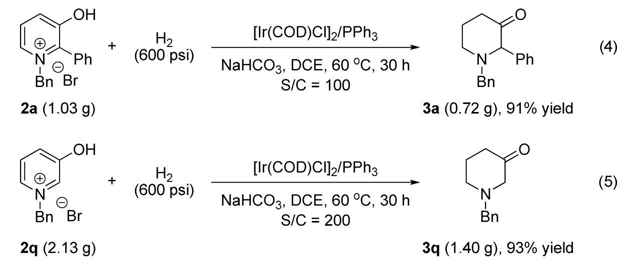
entry	R	product	yield (%)[b]
1	Ph	**3r**	85
2	3-MeC_6H_4	**3s**	88
3	4-MeOC_6H_4	**3t**	85
4	3-ClC_6H_4	**3u**	88
5	4-BrC_6H_4	**3v**	86
6	$3\text{-MeO}_2CC_6H_4$	**3w**	83
7[c]	Me	**3x**	84

[a]Conditions: **2** (0.20 mmol), $[Ir(COD)Cl]_2$ (0.5 mol %), PPh_3 (2.2 mol %), H_2 (600 psi), $NaHCO_3$ (0.20 mmol), DCE (3.0 mL), 50 °C, 20 h. [b]Isolated yield. [c]The reaction temperature was 60 °C.

complete conversion regardless of the position and electronic effect of substituents on the phenyl ring (**3r**−**w**). Notably, the 4-methyl-substituted product **3x** could also be obtained in good yield. **3x** was a useful intermediate en route to Xeljanz for the treatment of rheumatoid arthritis.[16]

To further highlight the practical utility of our approach, selective hydrogenation of **2a** was performed on a gram scale, with excellent selectivity and yields maintained (Scheme 3). The

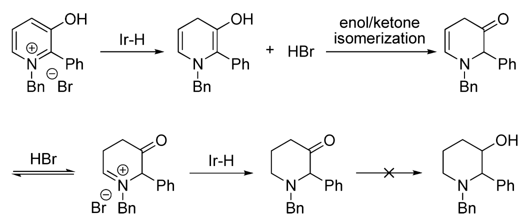
Scheme 3. Gram Scale Experiment



benzyl group was easily removed through Pd/C-catalyzed hydrogenolysis (see the Supporting Information). Using Noyori's ruthenium catalyst, the piperidin-3-one **3a** could be transformed to chiral piperidin-3-ol,[1a] which could be converted to L-733,060 through the known etherification and deprotection.[17] Under the similar reaction conditions, the hydrogenation of **2q** could also be carried out on a gram scale. Further decreasing the catalyst loading to 0.5 mol % had no impact on the conversion. The desired product **3q** was obtained in 93% isolated yield (eq 5). Piperidin-3-one **3q** is an important intermediate for the synthesis of CC chemokine receptor-3 antagonist.[18]

With the highly selective catalyst system in hand, we also examined the asymmetric hydrogenation of 3-hydroxy-pyridinium salts **2a** using a chiral diphosphine ligand. Unfortunately, the product **3a** was obtained in racemic form. This might be ascribed to the fast enol/ketone isomerization, which is the enantio-controlling step (vide infra). Based on the experimental results and general hydrogenation mechanism of pyridine,[19] a plausible reaction pathway was proposed (Scheme 4). The

Scheme 4. Proposed Reaction Mechanism



substrate may first undergo 1,4-hydride addition to give a 1,4-dihydropyridine intermediate, followed by a fast enol/ketone isomerization. The stereogenic center is built without the participation of the catalyst. Subsequent hydrogenation of the enamine or iminium intermediate delivers the final ketone products. The low activity for the iridium catalyst to C═O keeps the ketone as the major product.

In conclusion, we have developed an expedient method for the synthesis of piperidin-3-ones from readily available 3-hydroxypyridinium salts. A variety of 2- and 4-substituted piperidin-3-ones could be obtained in high yields. The piperidin-3-ones are important intermediates for the synthesis of bioactive molecules and the prevalent structural motifs in pharmaceutical agents. The mild reaction conditions, high chemoselectivity, and easy scalability make this reaction highly practical. Further efforts to realize the hydrogenation of other pyridinols and explore the asymmetric version are ongoing in our laboratory. The results will be reported in due course.

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ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, and NMR spectra. 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 interest.

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