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Efficient and Chemoselective Reduction of Pyridines to Tetrahydropyridines and Piperidines *via* Rhodium-Catalyzed Transfer Hydrogenation

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Abstract: Promoted by iodide anion the rhodium complex dimer, $[Cp^*RhCl_2]_2$, catalyzes efficiently the transfer hydrogenation of various quaternary pyridinium salts under mild conditions, affording not only piperidines but also 1,2,3,6-tetrahydropyridines in a highly chemoselective fashion, depending on the substitution pattern at the pyridinium ring. The reduction is conducted in azeotropic formic acid/triethylamine ($HCOOH\text{-}Et_3N$) mixture at 40 °C, with catalyst loadings as low as 0.005 mol% being feasible.

Keywords: piperidines; pyridines; rhodium catalysts; tetrahydropyridines; transfer hydrogenation

Piperidines, which structurally exist in numerous natural products and synthetic bioactive compounds, have attracted a tremendous amount of attention in the chemical and pharmaceutical industries.[1] For instance, among well-known prescription drugs are the piperidine derivatives Risperdal used for treatment of schizophrenia,[2] Concerta for ADHD,[3] Aricept for Alzheimer's disease,[4] Paroxetine as an antidepressant[5] and Fentanyl as a pain reliever[6] (Figure 1).

Given their immense pharmaceutical utilities, the synthesis of piperidines has been extensively studied.[1c,e–i] Hydrogenation of easily accessible pyridines provides probably the most economic and efficient route for accessing piperidines.[7] Over the past eighty years, a variety of heterogeneous catalysts, such as PtO_2, Raney Ni, RuO_2, Rh/C and Pd/C, have been used to fully reduce pyridines with H_2;[7–9] but most of these catalysts are of low activity and selectivity and require harsh reaction conditions. Recently, several homogeneous Rh, Ir and Ru complexes[10] and an organocatalyst[11] have been reported to catalyze the hydrogenation.[12] However, special activating groups generally need to be installed on the pyridines and a relatively high catalyst loading is necessary.

Partial hydrogenation of pyridines to give tetrahydropyridines is even more interesting, since the result-

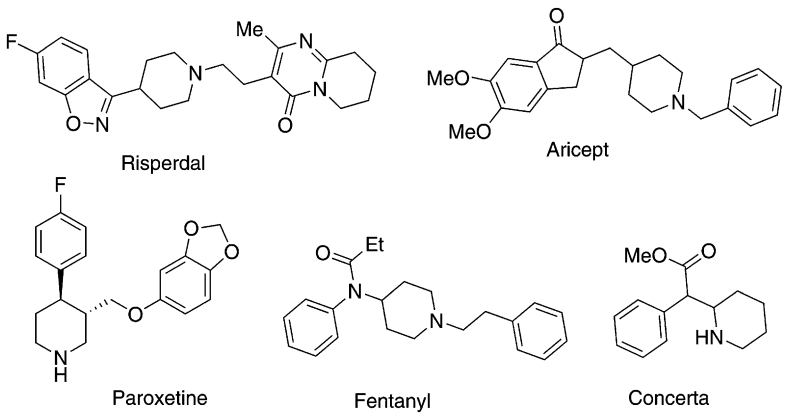
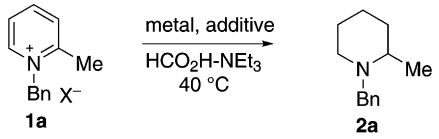


Figure 1. Piperidine derivatives as prescription drugs.

ing unsaturated piperidines can be further transformed into other value-added products *via* many well-established reactions, such as asymmetric hydrogenation, epoxidation, dihydroxylation, and allylic substitution and isomerization.[13] Consequently, a huge number of reactions have been carried out for the partial reduction of pyridines.[8,14] In almost all of the cases, however, stoichiometric reducing reagents, such as $NaBH_4$, $LiAlH_4$ and metal Na, are employed. Apart from being hazardous and generating copious amounts of toxic waste, these reagents are characterized with poor selectivity, which limits their application in modern synthesis. A few examples of the partial hydrogenation of pyridines with heterogeneous catalysts are also known, most of which afford 2,3-unsaturated piperidines bearing electron-withdrawing groups.[15] Therefore, it remains a great challenge to reduce pyridines in a general, efficient, selective and operationally benign manner. Herein, we disclose a simple, effective catalytic system for the transfer hydrogenation of pyridines. *Notably, this protocol affords not only piperidines, but also the 3,4-unsaturated variants highly chemoselectively.*

We recently reported that, promoted by iodide, the simple dimeric complex $[Cp^*RhCl_2]_2$ allows for the highly efficient transfer hydrogenation of quinolines, isoquinolines and quinoxalines using the azeotropic mixture HCOOH-Et_3N as reductant.[16] Following this success, we attempted to apply the $[Cp^*RhCl_2]_2$-I^- catalyst to the reduction of pyridines. No reaction was observed with the model substrate 2-methylpyridine (pK_a 6.0), which is expected to be protonated by formic acid (pK_a 3.6). Delightfully, we found that quaternized pyridines underwent the reduction readily. Given the simplicity of quaternization with benzyl halides and the importance of benzyl-protected piperidines, we set out to examine the catalysis with *N*-benzyl-2-picoline bromide, which can be conveniently prepared by alkylation of 2-picoline with benzyl bromide. As can be seen from Table 1, catalyzed by only 0.005 mol% $[Cp^*RhCl_2]_2$, the picoline bromide was reduced in HCOOH-Et_3N at 40 °C, affording *N*-benzylpiperidine in 85% isolated yield (Table 1, entry 1). As with the reduction of other *N*-heterocycles,[16] the iodide salt KI again shows a remarkable accelerating effect on the reduction (Table 1, entries 1 *vs.* 2). Although the reaction proceeds without the iodide, the same result can only be obtained by using a much higher catalyst loading (Table 1, entry 3). The concentration of the iodide salt affects the reduction rates, with higher product yields obtained using one equivalent of KI (Table 1, entry 4), under which a turnover number (TON) of 9000 is generated. To the best of our knowledge, this is the highest TON value ever reported in the catalytic reduction of pyridines. However, a higher concentration of I^- deactivates the catalyst (Table 1, entry 5), resembling what we reported before.[16] The yield was slightly improved when increasing the catalyst loading to 0.05 mol% (Table 1, entry 6). Control experiments show that no reduction occurs without the rhodium, and other metal compounds are ineffective (Table 1, entries 7–10). As expected, when picolinium iodide was used, **2a** was obtained in excellent yield without adding any KI (Table 1, entry 11). We note, however, that pyridinium iodide salts are generally much more difficult to access than the bromides. In contrast, no reaction was observed when the anion of the picolinium salt was replaced with a non-coordinating anion, SbF_6^- (Table 1, entry 12), showing again the importance of the coordinating anion to the catalytic activity.[16]

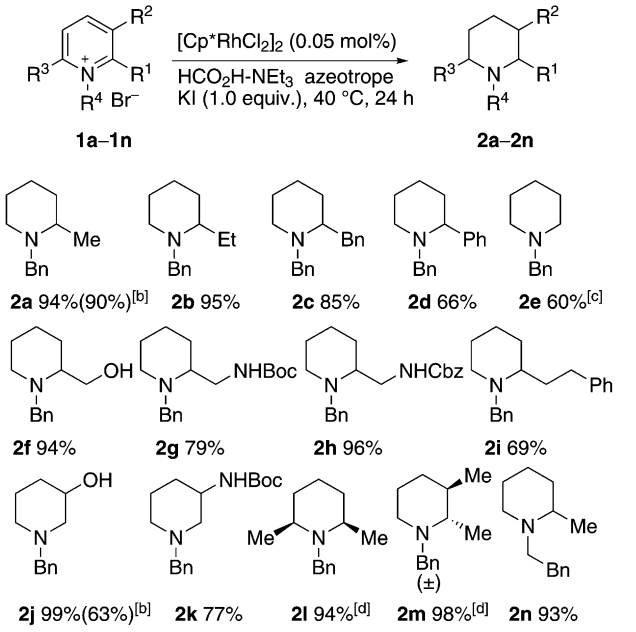
Table 1. Effect of metal compounds and iodide on the transfer hydrogenation of **1a**.[a]



Entry	X	Metal, mol%[b]	Additive, equiv.	Yield[c]
1	Br	[Rh], 0.005	KI, 0.1	85
2	Br	[Rh], 0.005	none	9
3	Br	[Rh], 0.5	none	84
4	Br	[Rh], 0.005	KI, 1.0	90
5	Br	[Rh], 0.005	KI, 3.0	10
6	Br	[Rh], 0.05	KI, 1.0	94
7	Br	none	KI, 1.0	NR[d]
8	Br	[Ir], 0.5	none	4
9	Br	[Ru], 0.5	none	NR[d]
10	Br	$RhCl_3$, 1.0	none	NR[d]
11	I	[Rh], 0.005	none	92
12	SbF_6	[Rh], 0.5	none	NR[d]

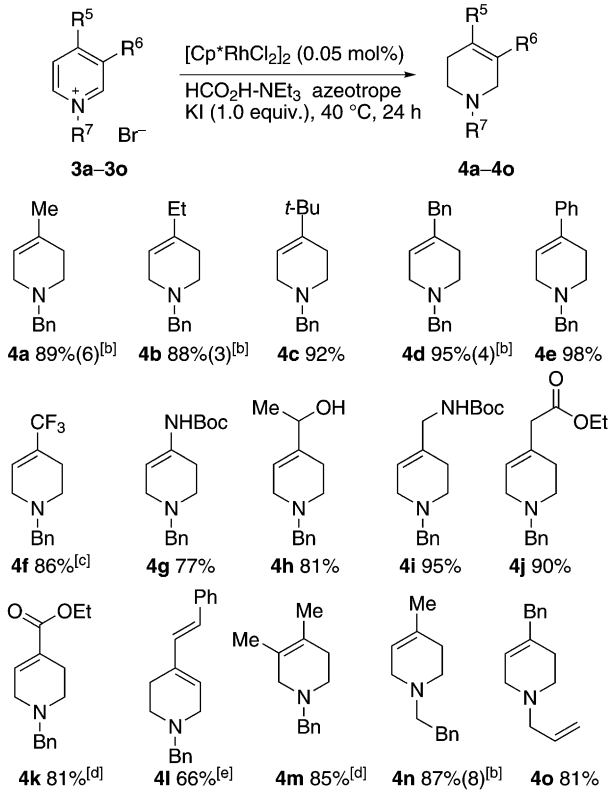
[a] Reaction conditions: pyridinium salt **1a** (0.5 mmol), HCO$_2$H-NEt$_3$ azeotrope solution (5 mL), 40 °C, 24 h under N_2, Bn = benzyl.
[b] [Rh] = $[Cp^*RhCl_2]_2$, [Ir] = $[Cp^*IrCl_2]_2$ and [Ru] = [$RuCl_2$(*p*-cymene)]$_2$.
[c] Isolated yields.
[d] No reaction or no desired product observed.

Having the optimized reaction conditions in hand, a variety of pyridinium salts were subjected to transfer hydrogenation with 0.05 mol% $[Cp^*RhCl_2]_2$. As shown in Scheme 1, a range of mono- or disubstituted pyridiniums were reduced, affording the corresponding *N*-benzylpiperidines in good to excellent yields. Thus, 2-alkyl-substituted pyridiniums underwent smooth hydrogenation to give 2-alkylpiperidines in high yields (Scheme 1, **2a**–**2c**). A lower yield was obtained with the 2-phenylpiperidine (**2d**), probably due to steric demand of the phenyl ring and/or its stabilization of the intermediate iminium C=N bond (*vide infra*). Surprisingly somehow, the unsubstituted pyridinium gave a mixture of 3,4-unsaturated piperidine and piperidine, with the latter (**2e**) accounting for



[a] All reactions were carried out under the standard conditions: **1** (0.5 mmol), $[Cp^*RhCl_2]_2$ (0.25 μmol), KI (0.5 mmol), HCO_2H-NEt_3 azeotrope solution (5 mL), 40 °C, N_2, 24 h; isolated yields are given below the product structures.
[b] Data in brackets were obtained with 0.005 mol% catalyst.
[c] 99% total isolated yield; the product was a mixture of **2e** and 3,4-unsaturated piperidine in a ratio of 3:2.
[d] **2l**, *cis/trans* = 3.2:1, determined by ^{1}H NMR; **2m**, *trans/cis* > 99:1, determined by NOE analysis.

Scheme 1. Transfer hydrogenation of pyridinium salts to piperidines.[a]



[a] Reactions were carried out under the standard conditions given in Scheme 1.
[b] Yield of fully reduced product is given in the bracket (determined by ^{1}H NMR).
[c] 0.5 mol% catalyst was used.
[d] 0.25 mol% catalyst was used.
[e] The conformation was determined by NOE analysis.

Scheme 2. Partial transfer hydrogenation of 4-substituted pyridinium salts.[a]

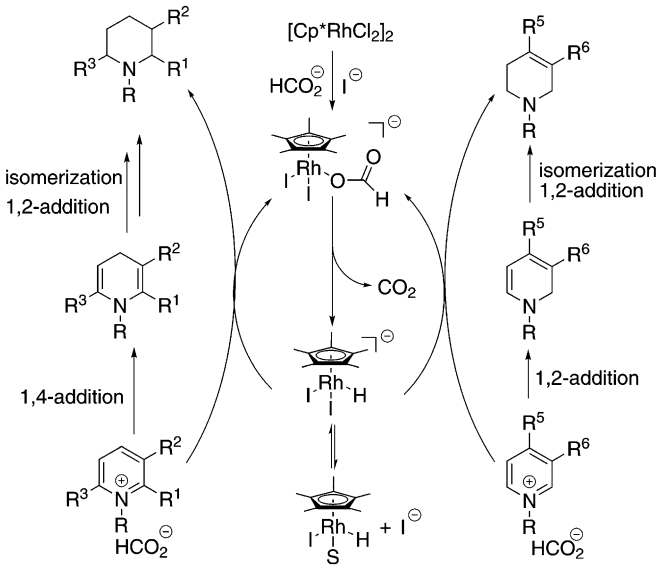
60% of the mixture. The formation of the unsaturated piperidine is likely a result of competing 1,2-hydride addition (*vide infra*). Most interestingly, substrates bearing hydroxy and protected amino groups at either 2 or 3 positions were tolerated, generating synthetically valuable amino alcohols and diamines (**2f**–**h**, **j**, **k**). For instance, **2j** and **2k** have found applications in the pharmaceutical industry as cyclic β-amino alcohols and diamines.[17] However, a conjugated C=C double bond at the 2-postion was fully reduced, leading to **2i** probably *via* 1,4-hydride addition beginning at the carbon α to the Ph group. Notably, 2,3-disubstituted pyridinium can be hydrogenated to piperidine exclusively as the *trans* isomer (**2m**), whilst the 2,6-disubstituted pyridinium affords *cis* piperidine as the major product (**2l**). Non-benzyl quaternized pyridine is also viable. Thus, the *N*-phenylethylpiperidine **2n**, an analogue of a well-known σ receptor antagonist for treating methamphetamine abuse,[18] is generated from the corresponding pyridinium salt in excellent yield.

On applying the catalysis to 4-substituted pyridiniums we met with a surprise. Thus, under the same conditions as above, the reduction of 4-methylpyridinium **3a** afforded primarily the 3,4-unsaturated piperidine **4a** (Scheme 2). Prompted by this finding while bearing in mind the importance of such products, we subsequently examined the hydrogenation of a series of 4-substituted pyridiniums. The results are found in Scheme 2. To our delight, most of 4-substituted pyridiniums were reduced with high or exclusive selectivities toward the 3,4-unsaturated piperidine products. Thus, pyridiniums bearing different 4-alkyl substituents were hydrogenated with excellent yields (**4a**–**d**), with a bulkier substituent affording a higher chemoselectivity favouring **4**. For instance, in the case of **4c**, no fully reduced product was observed. The same is also true with 4-phenyl-substituted pyridinium **3e**, which led to **4e** in excellent yield. Of particular note is that pyridiniums bearing electron-withdrawing and electron-donating groups (**3f**, **g**) and other functionalities, such as hydroxy (**3h**), ester (**3j**, **k**) and protected amine (**3i**), were viable as well, being reduced with excellent chemoselectivities and high yields. In contrast to the reduction of **1i**, the conjugated C=C double bond in **3l** was retained. The 4-styryl-substituted **4l**

was isolated in 66% yield, exclusively in the s-*cis* conformation. Furthermore, 3,4-disubstituted pyridinium (**3m**) was also reduced, although a higher catalyst loading (0.25 mol%) was required. Finally, replacing the benzyl group with phenylethyl did not affect much the yield (**4n**), and more interestingly, the benzyl could also be replaced with an allyl group (**4o**), which would be problematic in heterogeneous hydrogenation. The presence of alkene, diene, hydroxy, amino, ester and allyl units in these piperidines opens a vast potential for further reactions, as indicated before. We note that 3,4-unsaturated piperidines can be accessed generally only through reduction with boron hydrides.[8]

To further showcase the utility of this new protocol, we carried out the synthesis of compound **4e** on a gram scale. 4-Arylpiperidines are a valuable structural unit found in a number of drug discovery programs for potential treatment of symptoms such as asthma, hypertension, depression, cocaine abuse, benign prostatic hyperplasia, estrogen-related disorders, and Alzheimer's and Parkinson's diseases.[19] Commercial 4-phenylpyridine was quaternized easily with benzyl bromide affording **3e** in quantitative yield. Transfer hydrogenation of **3e** (1.0 g) in the HCO_2H-NEt_3 azeotrope with an even lower catalyst loading of 0.0125 mol% (0.25 mg) in air provided the 3,4-unsaturated piperidine product **4e** in 97% isolated yield. This appears to us to be the most efficient way for accessing this type of compound, regarding cost, effectiveness, practicability and scalability.[19,20] It is also worth noting that for most reactions in Scheme 1 and Scheme 2, the work-up simply involves direct extraction after basifying the reaction mixture without further purification, due to the high solubility of pyridinium and other salts in aqueous solution.

A plausible mechanism explaining the role of iodide and the observed chemoselectivity is shown in Scheme 3. As suggested before,[16,21] the substrate is likely to be reduced with an anionic diiodo Rh–H hydride species. Both the iodide and anionic charge would render the hydride more hydridic, facilitating its transfer to the pyridinium. However, excess iodide salt is needed in order to suppress the dissociation of iodide anion from the active hydride species.[16,22] In the absence of a 4-substituent, the hydride adds preferentially at the 4 position initially (i.e., 1,4-addition); the resulting enamine isomerizes to an iminium species and is then reduced *via* a 1,2-hydride addition. When the 4 position is substituted, 1,4-addition becomes impossible. Instead, 1,2-addtion takes place to give 1,2-dihydropyridine; isomerization of the resulting enamine followed by another 1,2-adddition affords the *N*-substituted 1,2,3,6-tetrahydropyridines **4**. Consistent with this picture, the 2,4,6-positions of **2a** and the 2,6-positions of **4c** were deuterated when



Scheme 3. Plausible mechanism for the chemoselective transfer hydrogenation.

DCOOH-NEt_3 was used to reduce **1a** and **3c**, respectively (see the Supporting Information for details).

In conclusion, we have developed a simple, efficient protocol for the chemoselective reduction of pyridinium salts. A variety of piperidines and, more interestingly, 1,2,3,6-tetrahydropyridines were obtained with good to excellent yields, providing valuable intermediates and feedstocks for chemical, pharmaceutical and agrochemical synthesis.

Experimental Section

Typical Procedure

A carousel reaction tube containing a magnetic stirring bar, $[Cp^*RhCl_2]_2$ (0.16 mg, 0.25 μmol, measured using a DCM stock solution), *N*-benyl-2-methylpyridinium bromide (**1a**, 132 mg, 0.5 mmol) and potassium iodide (83 mg, 0.5 mmol) in 5 mL HCOOH-Et_3N azeotrope was sealed after degassing and placed in the carousel reactor. The reaction mixture was stirred at 40 °C for 24 h, cooled to room temperature and then basified with an aqueous solution of KOH. The resulting mixture was extracted with ethyl acetate (3 × 20 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure. Analytically pure **2a** was obtained after further drying under vacuum; yield: 94%.

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