Asymmetric Hydrogenation

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Iridium-Catalyzed Asymmetric Hydrogenation of Pyridinium Salts**

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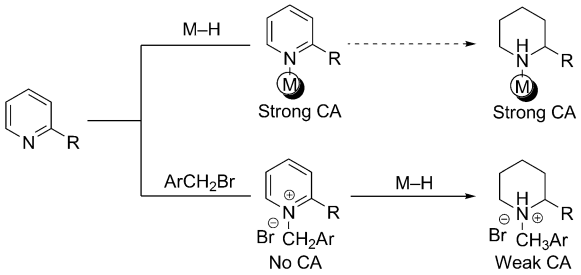
As one of the most straightforward and powerful approaches for the preparation of optically active compounds, asymmetric hydrogenation has been successfully used for different types of aromatic compounds, including quinolines, isoquinolines, quinoxalines, indoles, pyrroles, furans, imidazoles, and aromatic carbocyclic ring, with excellent enantioselectivities.[1–9] Despite these advances, direct hydrogenation of simple pyridines is still a challenge. The inherent problems are apparent: First, substrates and corresponding products that possess strong coordination ability might cause the deactivation of catalysts. Second, pyridines have a stabilizing aromatic structure that might impede the reduction. Therefore, only limited examples of hydrogenation of specific pyridine derivatives bearing powerful electron-withdrawing substituent at the 2- or 3-position have been previously described. In 2000, Studer et al. reported the first homogeneous rhodium-catalyzed asymmetric hydrogenation of pyridines, but only poor enantioselectivity was obtained.[10] Zhang and co-workers described an efficient three-step rhodium-catalyzed asymmetric hydrogenation of nicotinates.[11] Subsequently, the group of Rueping documented the first enantioselective organocatalytic transfer hydrogenation of 3-cyano- or carbonyl-substituted pyridines using Hantzsch esters as hydrogen sources,[12] and our group also employed [{Ir(cod)Cl}$_2$]/(*S*)-MeO-biphep/I$_2$ catalyst system for asymmetric hydrogenation of specific pyridines with excellent enantioselectivities.[13] Additionally, an elegant asymmetric hydrogenation of activated pyridines, that is, *N*-iminopyridinium ylides, was developed by Charette et al.[14] As chiral piperidines are important building blocks for the synthesis of biologically active molecules and natural products,[15] the development of an efficient strategy for the highly challenging hydrogenation of the simple pyridines is still of great significance.

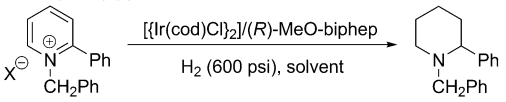
Iminium salts generally exhibit higher activity than the corresponding imines in hydrogenation,[15b–l,16] therefore we envisioned that the activation of simple pyridines as the corresponding *N*-benzyl-pyridinium bromides would effectively eliminate coordination ability of the substrate and thus the reactivity could be greatly enhanced. Moreover, the stoichiometric amount of hydrogen bromide generated in situ would effectively inhibit the coordination ability of the desired product through the formation of its piperidine hydrogen bromide salt (Scheme 1). Also, the benzyl protecting groups could be conveniently removed by hydrogenolysis. Herein, we disclose the iridium-catalyzed asymmetric hydrogenation of 2-substituted pyridinium salts with excellent enantioselectivity.



Scheme 1. The strategy for hydrogenation of simple pyridines. CA = coordination ability, M = metal.

Our investigation started with the asymmetric hydrogenation of *N*-benzyl-2-phenylpyridinium bromide using [{Ir(cod)Cl}$_2$]/(*R*)-MeO-biphep as the catalyst (Table 1). To our delight, when CH_2Cl_2 was employed as the solvent, the reaction proceeded smoothly to give the target product in 84% yield and a moderate enantioselectivity (66% *ee*; Table 1, entry 1). A survey of different solvents indicated that the 1:1 mixture of PhMe/CH_2Cl_2 was the best choice with

Table 1: Screening of solvents and counterions for asymmetric hydrogenation of 2-phenylpyridinium salt.[a]



1 **2**

Entry	Solvent	X	Yield [%][b]	*ee* [%][c]
1	CH_2Cl_2	Br	84	66
2	MeOH	Br	17	5
3	THF	Br	86	67
4	PhMe	Br	53	77
5	PhMe/CH_2Cl_2 2:1	Br	91	72
6	PhMe/CH_2Cl_2 1:1	Br	97	75
7	PhMe/CH_2Cl_2 1:2	Br	97	71
8	PhMe/CH_2Cl_2 1:1	I	13	57
9	PhMe/CH_2Cl_2 1:1	OTf	< 5	–

[a] **1** (0.25 mmol), [{Ir(cod)Cl}$_2$] (1 mol%), (*R*)-MeO-biphep (2.2 mol%), H_2 (600 psi), solvent (3 mL), 24 h, 28 °C. [b] Yield of the isolated product. [c] Determined by HPLC. cod = 1,5-cyclooctadiene, Tf = trifluoromethanesulfonyl.

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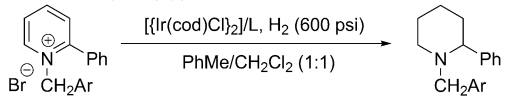
respect to the yield and enantioselectivity (Table 1, entries 2–7). Interestingly, replacement of the bromide counterion by iodide had a negative impact on reactivity and enantioselectivity (Table 1, entry 8). The trifluoromethanesulfonate anion also failed to promote the hydrogenation reaction (Table 1, entry 9).

Next, the influence of different activating groups on enantioselectivity was explored (Table 2). In particular, introducing an electron-withdrawing substituent (CO_2Me) at the 2-position of the benzyl group led to a significant increase

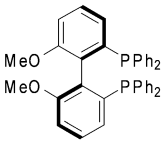
Table 2: Screening of activating groups and ligands for asymmetric hydrogenation of 2-phenylpyridinium salts.[a]



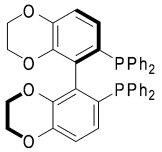
1 **2**

Entry	Ar	Ligand	Yield [%][b]	*ee* [%][c]
1	Ph	**L1**	97	75
2	2-$MeOC_6H_4$	**L1**	93	70
3	2-$(MeO_2C)C_6H_4$	**L1**	99	89
4	4-$(MeO_2C)C_6H_4$	**L1**	95	79
5	2-$(iPrO_2C)C_6H_4$	**L1**	98	92
6	2-$(iPrO_2C)C_6H_4$	**L2**	96	93
7	2-$(iPrO_2C)C_6H_4$	**L3**	98	93
8	2-$(iPrO_2C)C_6H_4$	**L4**	98	85
9	2-$(iPrO_2C)C_6H_4$	**L5**	98	91
10	2-$(iPrO_2C)C_6H_4$	**L6**	99	91

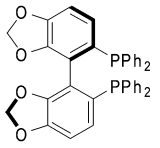
[a] **1** (0.25 mmol), $[\{Ir(cod)Cl\}_2]$ (1 mol%), **L** (2.2 mol%), H_2 (600 psi), $PhMe/CH_2Cl_2$ (1:1, 3 mL), 24 h, 28°C. [b] Yield of the isolated product. [c] Determined by HPLC.



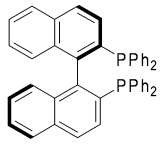
L1: (*R*)-MeO-biphep



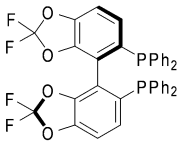
L2: (*R*)-synphos



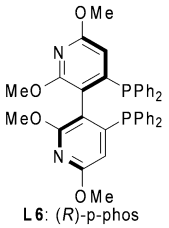
L3: (*R*)-segphos



L4: (*R*)- inap



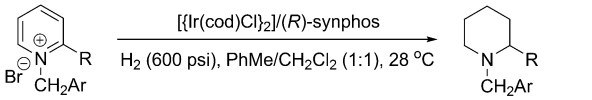
L5: (*R*)-difluorphos



L6: (*R*)-p-phos

of enantioselectivity (89% *ee*; Table 2, entry 3). The CO_2Me group at the 2-position is probably coordinated with catalyst, and thus is favorable to the control of enantioselectivity (Table 2, entry 3 versus 4). Gratifyingly, when there was a CO_2iPr group in the 2-position the enantioselectivity was improved slightly, possibly because of steric hindrance (Table 2, entry 5). Lastly, various commercially available chiral bisphosphine ligands were also evaluated (Table 2, entries 6–10). Among all the tested ligands, (*R*)-binap only gave 85% ee. Pleasingly, the electron-rich diphosphine ligands (*R*)-segphos and (*R*)-synphos displayed the highest enantioselectivity (Table 2, entries 6 and 7).

Table 3: Iridium-catalyzed asymmetric hydrogenation of 2-substituted pyridinium salts **1**.[a]



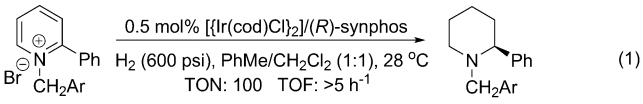
1 **2**

Entry	R	Yield [%][b]	*ee* [%][c]
1	Ph	99 (**2a**)	93 (*S*)
2	4-MeC_6H_4	99 (**2b**)	89 (−)
3	3-MeC_6H_4	88 (**2c**)	86 (−)
4	2-MeC_6H_4	82 (**2d**)	78 (−)
5	4-$MeOC_6H_4$	99 (**2e**)	92 (−)
6	3-$MeOC_6H_4$	93 (**2f**)	92 (−)
7	4-ClC_6H_4	95 (**2g**)	92 (−)
8	4-FC_6H_4	99 (**2h**)	93 (−)
9	2-naphthyl	99 (**2i**)	87 (−)
10[d]	4-$CF_3C_6H_4$	96 (**2j**)	93 (−)
11[d]	4-$tBuC_6H_4$	99 (**2k**)	84 (−)
12	4-PhC_6H_4	99 (**2l**)	91 (−)
13	Bn	99 (**2m**)	59 (+)
14[d]	*i*Pr	60 (**2n**)	65 (−)

[a] **1** (0.25 mmol), $[\{Ir(cod)Cl\}_2]$ (1 mol%), (*R*)-synphos (2.2 mol%), H_2 (600 psi), $PhMe/CH_2Cl_2$ (1:1; 3 mL), 24 h, 28°C. [b] Yields of the isolated product. [c] Determined by HPLC. [d] Determined by HPLC of product after derivatization with $LiAlH_4$. Bn = benzyl.

With the highly active catalytic system established, we turned our attention to examine the scope of substrates (Table 3). As expected, various substrates were performed very well under the standard reaction conditions. The electronic properties of the substituent on the aromatic ring had little effect on the catalytic activity and enantioselectivity (Table 3, entries 5 and 10). However, presumably as a result of steric hindrance, the substrate **1d** containing a substituent at the *ortho* position of the aromatic ring resulted in diminished yield and *ee* value (Table 3, entry 4). Notably, although the 2-alkylpyridine derivatives were suitable reaction partners, only moderate enantioselectivity were obtained (Table 3, entries 13 and 14).

To further evaluate the practical utility, the hydrogenation of *N*-benzyl-2-phenylpyridinium bromide (**1a**) was carried out on gram scale, and the desired product was furnished with 93% yield and 92% *ee* [Eq. (1); S/C = substrate/catalyst, TOF = turnover frequency, TON = turnover number].

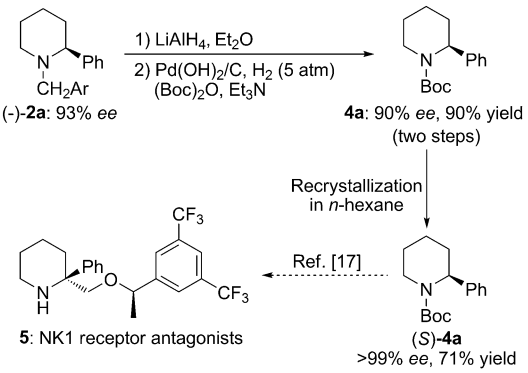


1a: 1.030 g
S/C = 100

2a: 93% yield (>95% conv.)
92% *ee*

(1)

To broaden the application of our methodology, we were keen to explore the formal synthesis of piperidine **5**, an orally active NK1 receptor antagonist (Scheme 2). Reduction of **2a** with lithium aluminum hydride gave the product **3a**, and subsequent hydrogenolysis and protection yielded **4a** with up to >99% *ee* after a single crystallization. **4a** was the key intermediate for the formal synthesis of the NK1 receptor



Scheme 2. The formal synthesis of NK1 receptor antagonist **5**. Boc = *tert*-butyloxycarbonyl.

antagonist[17] **5** reported in literature. The absolute configuration of **4a** was assigned to be *S* by comparison of the sign of the observed optical rotation with the reported data.[18]

In conclusion, we have successfully developed a highly efficient iridium-catalyzed hydrogenation of 2-substituted pyridinium salts, to provide chiral piperidines with high enantioselectivity. The key feature of this strategy was the activation of simple pyridines as the pyridinium bromide, thus efficiently avoiding inhibition of the catalyst by the substrate and improving the reactivity of the substrate. Moreover, the stoichiometric hydrogen bromide generated in situ is believed to effectively inhibit coordination ability of the desired product. Efforts to expand this strategy to other heteroaromatic compounds are underway in our laboratory.

Experimental Section

Typical procedure for asymmetric hydrogenation of pyridinium salt: In a nitrogen-filled glove box, a mixture of [{Ir(cod)Cl}$_2$] (1.7 mg, 0.0025 mmol) and (*R*)-SynPhos (3.5 mg, 0.0055 mmol) in PhMe/CH_2Cl_2 (1:1, 1.0 mL) was stirred at room temperature for 20–30 min, the mixture was transferred by a syringe to a stainless steel autoclave, in which substrate **1** (0.25 mmol) had been placed beforehand. The hydrogenation was performed at 28 °C under H_2 (600 psi) for 20–24 h. After carefully releasing the hydrogen, saturated sodium carbonate was added and the mixture was stirred for 15–30 min. The organic layer was separated and extracted with CH_2Cl_2 twice, and the combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. Purification was performed on a silica gel column eluted with hexane/EtOAc (10:1) to give the desired product. The enantiomeric excesses were determined by HPLC on a chiral stationary phase.

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