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Iridium-Catalyzed Asymmetric Hydrogenation of 2-Pyridyl Cyclic Imines: A Highly Enantioselective Approach to Nicotine Derivatives

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Supporting Information

ABSTRACT: A highly efficient asymmetric hydrogenation of cyclic imines containing a pyridyl moiety was established by using iridium catalysts with chiral spiro phosphine-oxazoline ligands. This process will facilitate the development of new nicotine-related pharmaceuticals. The introduction of a substituent at the *ortho* position of the pyridyl ring to reduce its coordinating ability ensures the success of the hydrogenation and excellent enantioselectivity.

Chiral N-heterocycles, such as pyrrolidine and piperidine derivatives, are very common in alkaloid natural products and pharmaceuticals.[1] The list of the top 200 prescription drugs in the United States in 2010 included more than 30 pyrrolidine and piperidine derivatives.[2] Nicotine, nornicotine, anabasine, and other nicotine-related alkaloids have shown potential for the treatment of Parkinson's disease, Alzheimer's disease, and various other conditions.[3] However, these compounds are highly toxic and have the potential for abuse, so the development of low-toxicity nicotine analogues for use as drugs, pesticides, and other bioactive compounds is highly desirable. Examples of such analogues include ABT-418, a prototypical cholinergic channel activator for the potential treatment of Alzheimer's disease;[4] SIB-1508Y, a novel anti-Parkinsonian agent with selectivity for neuronal nicotinic acetylcholine receptors;[5] A-85380, a novel, highly potent nicotinic acetylcholine receptor ligand;[6] and imidacloprid, one of the most commonly used insecticides worldwide (Figure 1).[7]

Transition-metal-catalyzed asymmetric hydrogenation of cyclic imines is an ideal method for preparing chiral pyrrolidines, piperidines, and other unsaturated N-heterocycles because of its perfect atom economy, operational simplicity, and environmental friendliness. Thus, this reaction has attracted increasing research attention over the past several decades.[8] However, the transition-metal-catalyzed enantioselective hydrogenation of pyridyl-containing unsaturated compounds remains a great challenge because the strong coordinating ability of the pyridine moiety tends to deactivate transition-metal catalysts.[9] For example, although a chiral titanocene catalyst shows good to high enantioselectivity for the asymmetric hydrogenation of various cyclic imine substrates, the reaction of 2-(3-pyridyl)-pyrroline does not proceed.[10]

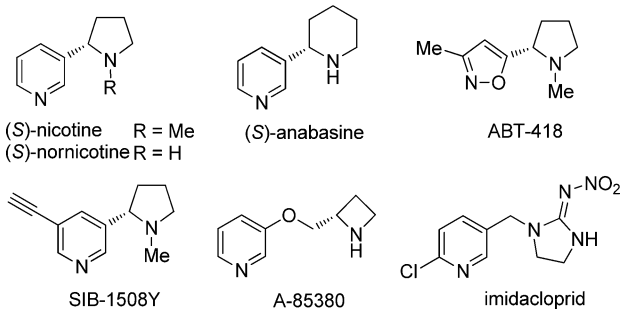

Figure 1. Nicotine and its analogues.

To overcome the challenge posed by transition-metal-catalyzed enantioselective hydrogenation of pyridyl-containing unsaturated N-heterocycles, we have developed a strategy we refer to as the "substituent-control strategy". Specifically, by introducing, at the position adjacent to the pyridine N atom, a substituent that either is present in the desired product or can be removed after the hydrogenation reaction, we can greatly reduce the coordination ability of the pyridine moiety and thus facilitate the asymmetric hydrogenation of pyridyl-containing unsaturated N-heterocycles. Here, we report the first highly enantioselective hydrogenation of pyridyl-containing cyclic imines catalyzed by iridium complexes with chiral spiro phosphine-oxazoline ligands.

Initially, we attempted to hydrogenate 2-(3-pyridyl)pyrroline under 50 atm of hydrogen in the presence of 10 mol % I_2 and 1 mol % chiral spiro iridium complexes (S_a,S)-**3**, which is known to catalyze the asymmetric hydrogenation of acyclic *N*-aryl ketimines,[11] but no reaction took place under any of the reaction conditions we investigated. In contrast, substrate **1a**,[12] which has a bromine substituent adjacent to the pyridine N atom, underwent hydrogenation catalyzed by (S_a,S)-**3a** to afford the desired amine product (**2a**) in 96% yield, although the enantiomeric excess (ee) was only 5% (Table 1, entry 1). We then systematically modified the catalyst by changing the substituent on the oxazoline ring and the *P*-aryl moieties of the spiro phosphine-oxazoline ligands (entries 2−6). Catalyst (S_a,S)-**3d**,[13] which has a phenyl group on the oxazoline ring and two 3,5-*tert*-butylphenyl groups on the P atom, proved to be the best catalyst, giving full conversion, a 98% yield of the desired product, and an ee of 96% (entry 4). Catalyst (S_a,R)-**3d**, a diastereoisomer of (S_a,S)-**3d**, was inactive (entry 7), indicating that the chiralities of (S_a,S)-**3d** were well matched. Various solvents could be used for this hydrogenation (entries 8−12), with 1,4-dioxane giving the best results (full conversion, 98%

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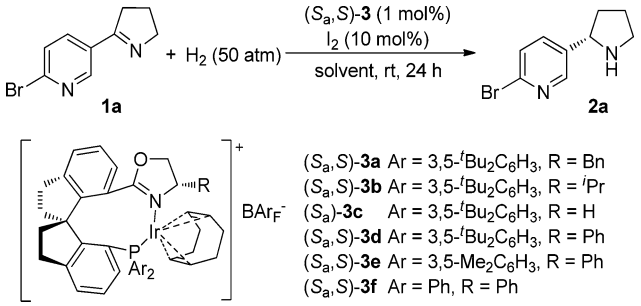
Table 1. Enantioselective Ir-Catalyzed Hydrogenation of 2-(6-Bromo-pyridin-3-yl)-1-pyrroline 1a: Optimization of Reaction Conditions[a]



entry	catalyst	solvent	conv (%)[b]	yield (%)[c]	ee (%)[d]
1	(S_a,S)-**3a**	THF	100	96	5
2	(S_a,S)-**3b**	THF	100	97	6
3	(S_a,S)-**3c**	THF	100	96	29
4	(S_a,S)-**3d**	THF	100	98	96
5	(S_a,S)-**3e**	THF	100	95	93
6	(S_a,S)-**3f**	THF	100	93	91
7	(S_a,R)-**3d**	THF	0	–	–
8	(S_a,S)-**3d**	1,4-dioxane	100	98	98
9	(S_a,S)-**3d**	Et_2O	90	85	90
10	(S_a,S)-**3d**	EtOAc	100	96	95
11	(S_a,S)-**3d**	CH_2Cl_2	89	87	88
12	(S_a,S)-**3d**	toluene	60	55	89

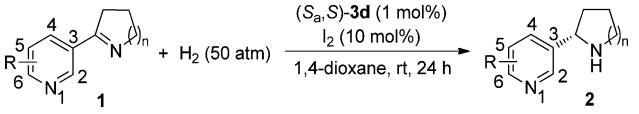
[a]Reaction conditions: 0.2 mmol of **1a**, [substrate] = 0.05 M, substrate/catalyst = 100, H_2 (50 atm), and 0.1 equiv of I_2 as additive. BAr_F is tetrakis[3,5-bis(trifluoromethyl)phenyl]borate. [b]Determined by ^1H NMR. [c]Isolated yield. [d]Determined by chiral HPLC analysis.

yield, and 98% ee; entry 8). I_2 was indispensable for the hydrogenation reaction, although its function is not clear.[14] The iodide additives, such as HI, KI, and LiI, are ineffective in this reaction. The absolute configuration of **2a** was determined as *S* by means of X-ray diffraction analysis of a single crystal.[13]

Various pyridine-containing pyrroline compounds were evaluated using the optimized reaction conditions (Table 2). In addition to the bromo substituent, other halogen substituents and methyl and methoxy substituents at the position adjacent to the N atom of the pyridine ring (**1b**–**1e**) also promoted the hydrogenation; the desired products were obtained with high yields and excellent enantioselectivities (entries 2–5). The presence of a second substituent on the pyridine ring had little effect on the yield or enantioselectivity (entries 6–9). This substituent-control strategy was also applicable for the asymmetric hydrogenation of 6- and 7-membered-ring cyclic imines; the corresponding N-heterocyclic compounds were obtained in high yields with good to excellent enantioselectivities (entries 10–13). Moreover, 2-(2-chloro-pyridin-4-yl)-1-pyrroline (**1n**) could also be hydrogenated with excellent yield (99%) and enantioselectivity (96% ee, Scheme 1). In contrast, 2-(6-bromo-pyridin-2-yl)-1-pyrroline (**1o**) was inert to the hydrogenation reaction; the two N atoms of **1o** may strongly coordinate the iridium to form a chelating complex and deactivate the catalyst.

This asymmetric hydrogenation reaction could be performed at the gram scale, which is advantageous for practical applications. For instance, the asymmetric hydrogenation of 1.08 g of imine **1a** ran smoothly in the presence of 1 mol % (S_a,S)-**3d** under 100 atm of H_2 in 18 mL of THF, producing (*S*)-**2a** in 95% yield with 93% ee.

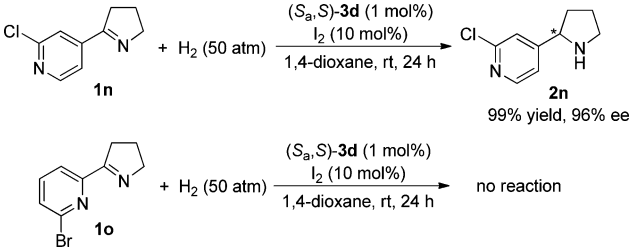
Table 2. Ir-Catalyzed Asymmetric Hydrogenation of 2-(Pyridin-3-yl) Cyclic Imines[a]



entry	R	*n*	conv (%)	yield (%)	ee (%)
1	6-Br (**1a**)	1	100	98 (**2a**)	98
2	6-Cl (**1b**)	1	100	97 (**2b**)	96
3	6-F (**1c**)	1	100	95 (**2c**)	94
4	6-Me (**1d**)	1	98	91 (**2d**)	>99
5	6-OMe (**1e**)	1	95	90 (**2e**)	96
6	5-Me-6-Br (**1f**)	1	100	98 (**2f**)	96
7	5-Me-6-Cl (**1g**)	1	100	95 (**2g**)	94
8	5-Me-6-F (**1h**)	1	100	92 (**2h**)	90
9	5,6-Cl_2 (**1i**)	1	97	95 (**2i**)	94
10	6-Br (**1j**)	2	100	93 (**2j**)	88
11	6-Cl (**1k**)	2	100	91 (**2k**)	81
12[b]	6-OMe (**1l**)	2	100	90 (**2l**)	91
13[c]	6-Br (**1m**)	3	93	85 (**2m**)	75

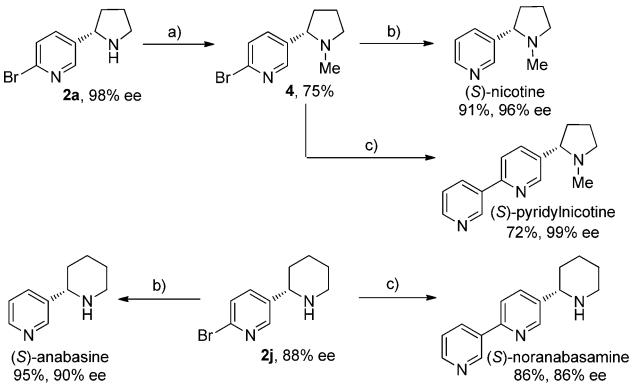
[a]Reaction conditions and analysis were similar to those in Table 1, entry 8 unless otherwise noted. [b]1.5 mol % catalyst was used. [c](S_a,S)-**3e** was used as catalyst.

Scheme 1. Asymmetric Hydrogenation of 1n and 1o



To demonstrate the utility of this asymmetric hydrogenation reaction, we synthesized four natural alkaloids, namely, (*S*)-nicotine, (*S*)-pyridylnicotine, (*S*)-anabasine, and (*S*)-noranabasmine, from the corresponding hydrogenation products (Scheme 2). Specifically, 6-bromonicotine (**4**) was obtained in 75% yield by methylation of **2a** with formaldehyde and formic acid.

Scheme 2. Total Synthesis of Chiral Pyrrolidine and Piperidine Alkaloids[a]



[a](a) HCHO/HCOOH, 80 °C; (b) Pd/C (2 mol %), H_2 (1 atm), MeOH, rt; (c) 3-PyB$(OH)_2$ (1.1 equiv), $Pd(PPh_3)_4$ (2.5 mol %), aq. Na_2CO_3 (2 M), DME/EtOH.

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Compound **4** was then transformed into (*S*)-nicotine with 96% ee by means of Pd-catalyzed debromination under hydrogenation conditions.[15] (*S*)-Pyridylnicotine,[16] an alkaloid isolated from a Colombian dendrobatid frog, was prepared by means of Pd-catalyzed cross-coupling between **4** and pyridin-3-yl boronic acid (commercially available) in 72% yield with 99% ee. Similarly, **2j** was readily transformed to (*S*)-anabasine and (*S*)-noranabasmine with high yields and no decrease in the ee value.[17] To the best of our knowledge, these are the first catalytic enantioselective syntheses of (*S*)-pyridylnicotine and (*S*)-noranabasmine. In these syntheses, the bromo substituent on the pyridine ring of the substrates not only promoted the asymmetric hydrogenation of the pyridyl-containing cyclic imines but also provided a locus for the highly efficient synthesis of nicotine analogues via simple transformations. Given that several nicotine analogues exhibit attractive bioactivities,[18] this asymmetric hydrogenation reaction may facilitate the development of nicotine-related pharmaceuticals.

In conclusion, we achieved the first highly enantioselective hydrogenation of cyclic imines bearing a pyridyl group by using iridium catalysts with a chiral spiro phosphine-oxazoline ligand. The reaction provides a direct catalytic route to the synthesis of chiral nicotine analogues. The key to successful hydrogenation is the inclusion of an *ortho* substituent on the pyridyl ring of the substrates to reduce the coordinating ability of the pyridine N atom. Concise syntheses of the natural pyrrolidine and piperidine alkaloids (*S*)-nicotine, (*S*)-pyridylnicotine, (*S*)-anabasine, and (*S*)-noranabasmine demonstrated the potential applications of this asymmetric hydrogenation in organic synthesis, and the strategy can be expected to facilitate the exploration of nicotine-derived bioactive compounds.

■ ASSOCIATED CONTENT

Supporting Information

CIF data for (*S*)-**2a** and (S_a,*S*)-**3d**, experimental procedures, and characterization data. 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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