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Enantioselective Hydrogenation of Pyrrolo[1,2-*a*]pyrazines, Heteroaromatics Containing Two Nitrogen Atoms

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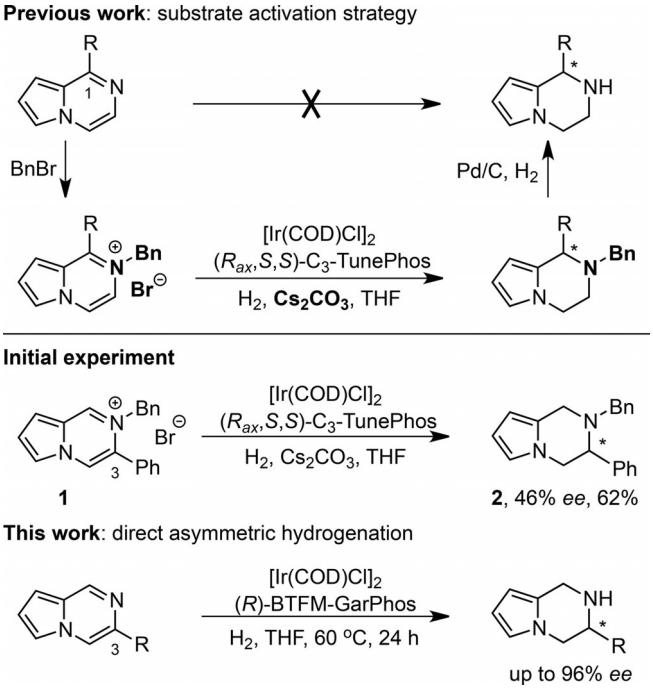
Abstract: An enantioselective iridium-catalyzed direct hydrogenation of heteroaromatics containing two nitrogen atoms, 3-substituted pyrrolo[1,2-*a*]pyrazines, has been successfully achieved, providing a facile synthesis of optically active 1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazines with up to 96% *ee*.

Keywords: asymmetric hydrogenation; iridium; pyrrolo[1,2-*a*]pyrazines; tetrahydropyrrolo[1,2-*a*]pyrazines

Enantiopure heterocyclic architectures with two or more heteroatoms in the ring core are ubiquitous in materials science, synthetic drugs and many bioactive natural products.[1] Consequently, the preponderance of such architectures has expedited the exploration of efficient and environmentally benign synthetic methods for their preparation.[2] The asymmetric hydrogenation of the corresponding heteroarenes, as one of the most atom-economic methodologies, has attracted a great deal of interest.[3,4] However, some difficulties including low activity, poor stereoselectivity or chemoselectivity and the relatively unstable products have hindered the development of this research field.[3b–d] Therefore, efforts towards the enantioselective hydrogenation of heteroaromatics containing multiple nitrogen atoms are focused on utilizing activation strategies, such as catalyst activation, substrate activation, or relay catalysis.[5] Nevertheless, some important progress has been achieved in the catalytic asymmetric hydrogenation of various heteroarenes containing two nitrogen atoms, for instance, imidazoles,[6] pyrazoles,[7] quinoxalines,[8] quinazolines,[9] pyrimidines,[10] pyrazines,[11] pyrrolo[1,2-*a*]pyrazines,[12] azaindoles,[13] naphthyridines,[14] 1,10-phenanthrolines,[15] and bisquinolines.[16] Notably, asymmetric hydrogenation of heteroaromatics bearing multiple heteroatoms is still far from being mature and there are also some problems that remain unsolved. Owing to the diversity of heteroaromatics bearing multiple heteroatoms, asymmetric hydrogenation of such compounds is still unexplored and full of challenges.

1,2,3,4-Tetrahydropyrrolo[1,2-*a*]pyrazines are prevalent skeletons that exist in natural products and are generally associated with pharmaceutical activities such as antiamnesic, antihypoxic, psychotropic, antihypersensitive and aldose reductase inhibitor activities.[17] Despite their impressive significance, there are only a few examples of efficient catalytic asymmetric methodologies for the preparation of medicinally interesting chiral 1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazines. In 2011, Li, Antilla and co-workers reported the first efficient method for the synthesis of chiral 1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazines through a chiral phosphoric acid-catalyzed asymmetric intramolecular aza-Friedel–Crafts reaction of *N*-aminoethylpyrroles with aldehydes.[18] Afterwards, an alternative method to chiral tetrahydropyrrolo[1,2-*a*]pyrazines was developed by our group through iridium-catalyzed asymmetric hydrogenation of 1-substituted pyrrolo[1,2-*a*]pyrazines *via* a substrate activation strategy (Scheme 1, *top*).[12] The activity and chemoselectivity for asymmetric hydrogenation of pyrrolo[1,2-*a*]pyrazines as well as the stabilities of 1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazines constitute the major stumbling blocks. The readily prepared pyrrolo[1,2-*a*]pyrazinium bromide avoided the coordination of substrates and reduced the energy for the dearomatization. Meanwhile, it is necessary to add a base to suppress the racemization pathway of the products.[12] Considering the importance of the 3-substituted tetrahydropyrrolo[1,2-*a*]pyrazine chiral skeleton,[17f] we investigated the feasibility of the asymmetric hydrogenation of 3-substituted pyrrolo[1,2-*a*]pyrazine through a substrate activation strategy. Initially, asymmetric hydrogenation of 2-benzyl-3-phenylpyrrolo[1,2-*a*]pyrazin-2-ium bromide (**1**) was run under the optimal conditions as reported

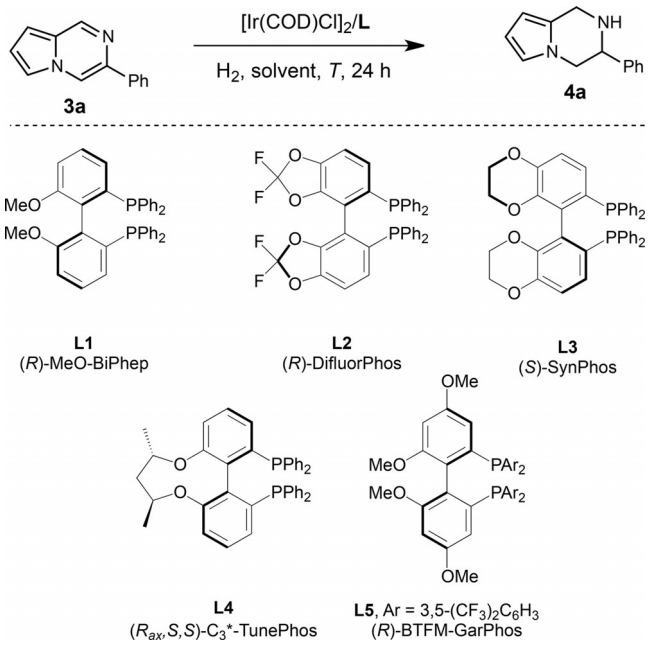


Scheme 1. Synthesis of chiral 1,2,3,4-tetrahydropyrrolo [1,2-*a*]pyrazines *via* asymmetric hydrogenation.

by us[12] and the desired product **2** was obtained in a moderate 46% *ee* and 62% yield (Scheme 1, *middle*). Due to the low activity and enantioselectivity, we next turned to explore the direct asymmetric hydrogenation of pyrrolo[1,2-*a*]pyrazines by looking for an efficient hydrogenation catalyst. Fortunately, an efficient catalytic system for the direct hydrogenation of 3-substituted pyrrolo[1,2-*a*]pyrazines was developed without preparation of onium salts or the introduction of a catalytic amount of additives to activate the catalyst (Scheme 1, *bottom*). Herein, a concise method to chiral 3-substituted 1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine derivatives was available through iridium-catalyzed asymmetric hydrogenation of 3-substituted pyrrolo[1,2-*a*]pyrazines with up to 98% yield and 96% *ee*.

As shown in Table 1, the readily available 3-phenylpyrrolo[1,2-*a*]pyrazine (**3a**) was selected as the model substrate for our study. Considering the use of halogen additives in the Ir-catalyzed asymmetric hydrogenation,[19] especially that the most commonly used iodine could significantly improve the performance of the catalyst, we conducted the asymmetric hydrogenation reaction employing $[Ir(COD)Cl]_2$/(*R*)-MeO-Biphep/I_2 as the catalyst and the desired product was furnished with full conversion and 51% *ee* (entry 1). Interestingly, there was almost no significant effect on the catalytic activity and enantioselectivity without the addition of iodine. (entry 2). It seems that it was unnecessary to introduce iodine into the catalyst system. Then, the solvent effects were examined without the addition of iodine (entries 2–6). With regard to the enantioselectivity and activity, tetrahydrofuran (THF) was chosen as the optimal solvent. The evaluation of commercially available chiral bisphosphine ligands demonstrated a dramatic improvement in the enantioselectivity to 94% with bulky (*R*)-BTFM-GarPhos but a small amount of substrate remained (entry 10). When the reaction temperature was raised to 60 °C, the substrate could be fully converted without any loss of enantioselectivity (entry 11). When trifluoroacetic acid (TFA) was added, the *ee* value was slightly decreased to 92% (entry 12). Finally, the optimal conditions were established as follows: [Ir(-

Table 1. The evaluation of the reaction parameters.[a]



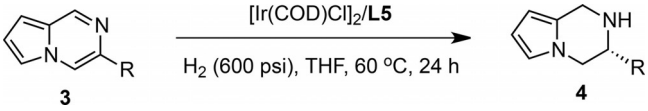
Entry	Solvent	Ligand	Conv. [%][b]	*ee* [%][c]
1[d]	THF	**L1**	>95	51
2	THF	**L1**	>95	54
3	1,4-dioxane	**L1**	>95	42
4	toluene	**L1**	>95	33
5	CH_2Cl_2	**L1**	91	59
6	$ClCH_2CH_2Cl$	**L1**	>95	53
7	THF	**L2**	>95	53
8	THF	**L3**	>95	69
9	THF	**L4**	>95	61
10	THF	**L5**	>95	94
11[e]	THF	**L5**	>95	94
12[f]	THF	**L5**	>95	92

[a] *Reaction conditions:* **3a** (0.20 mmol), $[Ir(COD)Cl]_2$ (1.0 mol%), **L** (2.2 mol%), solvent (3.0 mL), H_2 (600 psi), 40 °C, 24 h.
[b] Determined by ^1H NMR spectroscopy.
[c] Determined by chiral HPLC.
[d] I_2 (2.0 mol%).
[e] At 60 °C.
[f] TFA (1 equiv.).

COD)Cl]$_2$, (*R*)-BTFM-GarPhos, H_2 (600 psi), THF, 60 °C, 24 h.

With the optimized reaction conditions in hand, we explored the substrate scope of 3-arylpyrrolo[1,2-*a*]pyrazines. The results are depicted in Table 2. The

Table 2. The substrate scope.[a]



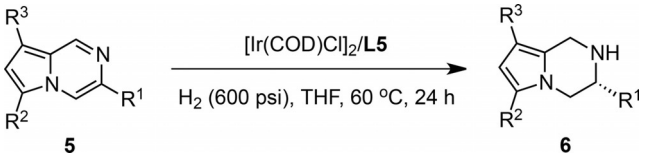
Entry	R	Yield [%][b]	*ee* [%][c]
1	Ph	98 (**4a**)	94 (*R*)
2	*p*-FC_6H_4	97 (**4b**)	92 (+)
3	*p*-ClC_6H_4	95 (**4c**)	91 (+)
4	*p*-BrC_6H_4	94 (**4d**)	90 (+)
5	*p*-MeC_6H_4	94 (**4e**)	90 (+)
6	*p*-$MeOC_6H_4$	97 (**4f**)	89 (+)
7	*m*-$MeOC_6H_4$	94 (**4g**)	91 (+)
8	*o*-$MeOC_6H_4$	92 (**4h**)	50 (+)
9	2-naphthyl	95 (**4i**)	91 (+)
10	*p*-PhC_6H_4	95 (**4j**)	89 (+)
11	cyclohexyl	95 (**4k**)	54 (+)

[a] *Reaction conditions:* **3** (0.20 mmol), [Ir(COD)Cl]$_2$ (1.0 mol%), **L5** (2.2 mol%), THF (3.0 mL), H_2 (600 psi), 60 °C, 24 h.
[b] Isolated yield.
[c] Determined by chiral HPLC.

presence of an electron-withdrawing group (F, Cl or Br) or electron-donating group (Me or MeO) on the aryl group has negligible influence on the activity and enantioselectivity (entries 2–6). A methoxy group at the *meta*-position or *para*-position slightly affected the reactivity and enantioselectivity (entries 6 and 7). Meanwhile, the introduction of an *ortho*-methoxy group led to an obvious decrease to 50% *ee* (entry 8). On changing the substituent at the C-3 position of the pyrrolo[1,2-*a*]pyrazine to a 2-naphthyl or 4-biphenylyl group, the reaction could also proceed smoothly (entries 9 and 10). The alkyl-substituted substrate **3k** was also subjected to the standard reaction conditions with full conversion and moderate enantioselectivity (54% *ee*, entry 11).

Afterwards, we examined the hydrogenation of pyrrolo[1,2-*a*]pyrazines with different substituents on the pyrrole ring (Table 3). It was found that different aryl or alkyl substituents at C-6 have insignificant effects on the reactivity (90–95%) and *ee* value (91–96%) (entries 1–7). Notably, hydrogenation of the *ortho*-substituted substrate at the C-6 position of pyrrolo[1,2-*a*]pyrazine **5b** provided the best enantioselectivity (96%, entry 2). Furthermore, the introduction of a bromine atom at the C-8 position of 6-phenyl-3-(*p*-tolyl)-pyrrolo[1,2-*a*]pyrazine gave the desired product

Table 3. The substrate scope.[a]

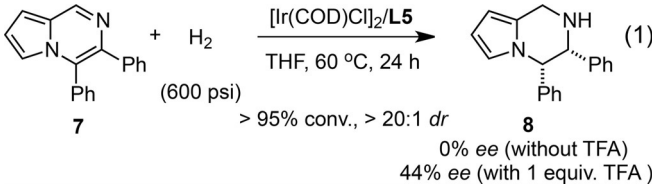


Entry	$R^1/R^2/R^3$	Yield [%][b]	*ee* [%][c]
1	Ph/Ph/H	95 (**6a**)	94 (−)
2	Ph/*o*-MeC_6H_4/H	90 (**6b**)	96 (+)
3	Ph/*m*-$MeOC_6H_4$/H	94 (**6c**)	93 (−)
4	Ph/*p*-$MeOC_6H_4$/H	95 (**6d**)	93 (−)
5	Ph/*p*-FC_6H_4/H	94 (**6e**)	94 (+)
6	Ph/Me/H	94 (**6f**)	92 (+)
7	*p*-MeC_6H_4/Ph/H	95 (**6g**)	93 (−)
8	*p*-MeC_6H_4/Ph/Br	94 (**6h**)	91 (+)

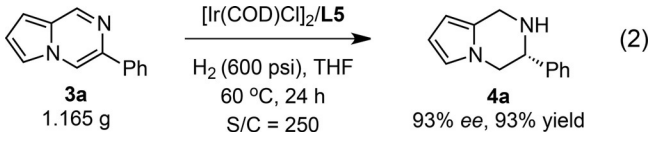
[a] *Reaction conditions:* **5** (0.20 mmol), [Ir(COD)Cl]$_2$ (1.0 mol%), **L5** (2.2 mol%), THF (3.0 mL), H_2 (600 psi), 60 °C, 24 h.
[b] Isolated yield.
[c] Determined by chiral HPLC.

6h with 91% *ee*, which possesses opportunities for further diversification (entry 8).

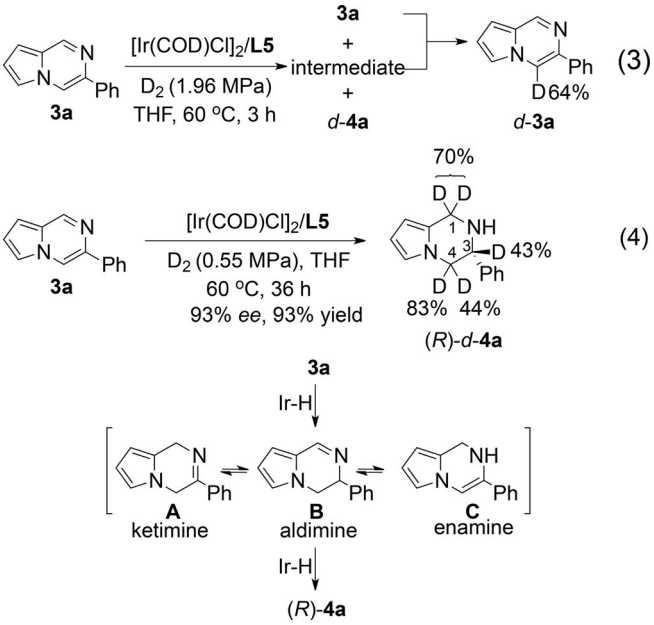
Next, the disubstituted 3,4-diphenylpyrrolo[1,2-*a*]pyrazine **7** was subjected to the above standard hydrogenation conditions, and racemic **8** was obtained albeit with excellent diastereoselectivity [Eq. (1)]. The following research indicated that the addition of a Brønsted acid could enhance the enantioselectivity, and a moderate 44% *ee* was obtained in the presence of TFA.



To further test the practicality of this methodology, the asymmetric hydrogenation of substrate **3a** was performed on a gram scale (1.165 g, 6.0 mmol) with 0.2 mol% of iridium catalyst at 60 °C for 24 h, providing the product **4a** in a 93% yield and 93% *ee* [Eq. (2)]. The absolute configuration of the derived product **4a**·TFA was determined to be *R* by X-ray crystallographic analysis.



To study the reaction pathway, an isotopic labeling experiment was carried out by deuteration of **3a** [Scheme 2, Eq. (3) and Eq. (4)]. A mixture of **3a**, **4a**,



Scheme 2. Isotopic labeling experiment and proposed reaction pathway.

and the possible intermediate was observed from the crude NMR spectroscopic and HR-MS analysis when the reaction was stopped at 3 h. However, the possible intermediate was oxidized to **3a** in the isolation process. Based on the deuterium content at the C-4 position (64%) of the recovered substrate, we supposed that the first step may be 3,4-reduction [Eq. (3)]. The results of Eq. (4) showed that in total three deuterium atoms were incorporated into the chiral product **4a** and the deuterated content at C-3 was only 43%. Tautomerization of the enamine-imine and imine-imine might occur during the hydrogenation process.

On the basis of the above results and the general hydrogenation mechanism of heteroaromatics,[3] a possible reaction pathway was proposed as shown in Scheme 2. The substrate **3a** first likely undergoes 3,4-hydride addition and subsequent tautomerization to form intermediates **A**, **B**, and **C**, followed by asymmetric hydrogenation to give the final product (*R*)-**4a**.

In conclusion, we have successfully developed an efficient iridium-catalyzed asymmetric hydrogenation of 3-substituted pyrrolo[1,2-*a*] pyrazines for synthesis of chiral tetrahydropyrrolo[1,2-*a*]pyrazines with up to 96% enantioselectivity. In this reaction, a readily prepared pyrrolo[1,2-*a*]pyrazinium salt or the addition of an additive is not essential. The mild conditions, short operation and easy scalability of this hydrogenation process make this methodology practical for further applications. Further efforts to achieve the asymmetric hydrogenation of other heteroaromatics containing two nitrogen atoms are ongoing in our laboratory.

Experimental Section

General Procedure: Asymmetric Hydrogenation of Pyrrolo[1,2-*a*]pyrazines

A mixture of $[Ir(COD)Cl]_2$ (1.35 mg, 0.002 mmol) and ligand **L5** (5.4 mg, 0.0044 mmol, 97%) was stirred in tetrahydrofuran (1.0 mL) at room temperature for 5 min in glove box. Then the pyrrolo[1,2-*a*]pyrazine (0.20 mmol) together with tetrahydrofuran (2.0 mL) were transferred to the reaction mixture. Then the vial was taken to an autoclave and the hydrogenation was conducted at a hydrogen pressure of 600 psi for 24 h at 60 °C. After carefully releasing the hydrogen, the autoclave was opened and the reaction solvent was evaporated under reduced pressure. Flash chromatography on silica gel gave the corresponding 1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine.

Acknowledgements

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