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Iridium-Catalyzed Asymmetric Hydrogenation of Tosylamido-Substituted Pyrazines for Constructing Chiral Tetrahydropyrazines with an Amidine Skelton

Kosuke Higashida,[a] Haruki Nagae,[a] and Kazushi Mashima[a,*]

[a] Department of Chemistry, Graduate School of Engineering Science, Osaka University, Toyonaka, Osaka 560–8531, Japan
Fax: (+81)-6-6850-6249; phone: (+81)-6-6850-6248; e-mail: mashima@chem.es.osaka-u.ac.jp

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Abstract: Dinuclear triply chloro-bridged iridium(III) complexes bearing chiral diphosphine ligands catalyze the asymmetric hydrogenation of tosylamido-substituted pyrazines to give the corresponding chiral tetrahydropyrazines with an amidine skeleton in high yield and with high enantioselectivity. Addition of *N*,*N*-dimethylanilinium bromide enhanced the catalytic activity of the iridium complexes and also increased the enantioselectivity of the products by trapping the hydrogenated amine products with HBr from *N*,*N*-dimethylanilinium bromide. The amidine skeleton of the products could be transformed to give chiral piperazinones and piperazines without loss of enantioselectivity.

Keywords: asymmetric hydrogenation; chiral tetrahydropyrazines; iridium catalyst; piperazines; piperazinones; pyrazines

Chiral piperazines and their derivatives, among the most common chiral six-membered cyclic amines, are abundant in natural products and bioactive compounds (Figure 1).[1] To prepare the chiral piperazines, intensive investigations were devoted to developing various synthetic protocols, including two component cyclization,[2] enantioselective addition of organometallic reagents supported by chiral amines,[3] and optical resolution.[4] These reactions require stoichiometric amounts of chiral compounds or multistep reactions, however, and thus more practical and straightforward synthetic methods are in high demand.

Asymmetric hydrogenation of *N*-heteroaromatic compounds provides a rational synthetic tool for constructing chiral cyclic amines: asymmetric hydrogenation of various *N*-heteroaromatic compounds,[5] such as quinoline,[6] isoquinoline,[7] quinoxaline,[8] quinazoline,[9] pyridine,[10] and pyrimidine,[11] have been achieved in high yield and with high enantioselectivity. Asymmetric hydrogenation of pyrazines to afford the corresponding chiral piperazines, however, is considered more difficult than hydrogenation of the aforementioned *N*-heteroaromatics due not only to the aromatic stabilization of pyrazines, but also to the high coordination ability of pyrazines and piperazines.

Pioneering work was accomplished by Fuchs who used rhodium complexes bearing chiral diphosphine ligands for the asymmetric hydrogenation of amide-substituted pyrazines to give the corresponding chiral amide-substituted piperazines with moderate enantioselectivity.[12] Recently, chiral iridium complexes were successfully applied to the asymmetric hydrogenation of pyrazinium units of the pyrrolo[1,2-*a*]pyrazinium salts, composed of a pyrrole ring fused to a pyrazinium salt ring,[13] and, quite recently, a chiral iridium catalyst under lower temperature (−20 °C) was reported to catalyze the asymmetric hydrogenation of *N*-benzylpyrazinium salts (Scheme 1).[14,15]

We have developed halide-bridged dinuclear complexes of iridium(III) and rhodium(III) bearing chiral diphosphine ligands to reduce various *N*-heteroaromatic compounds and simple olefins, respectively.[9,16] Notably, for the asymmetric hydrogenation of *N*-het-

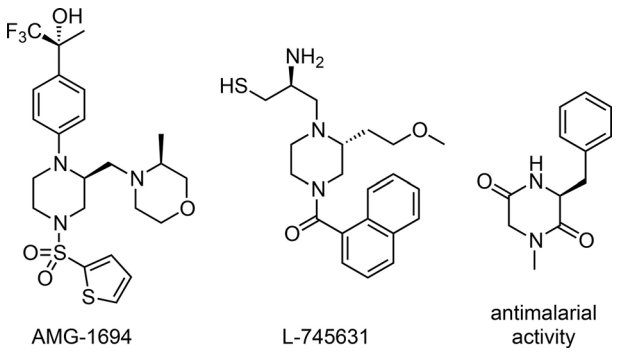

Figure 1. Some examples of bioactive compounds comprised of chiral piperazine derivatives.

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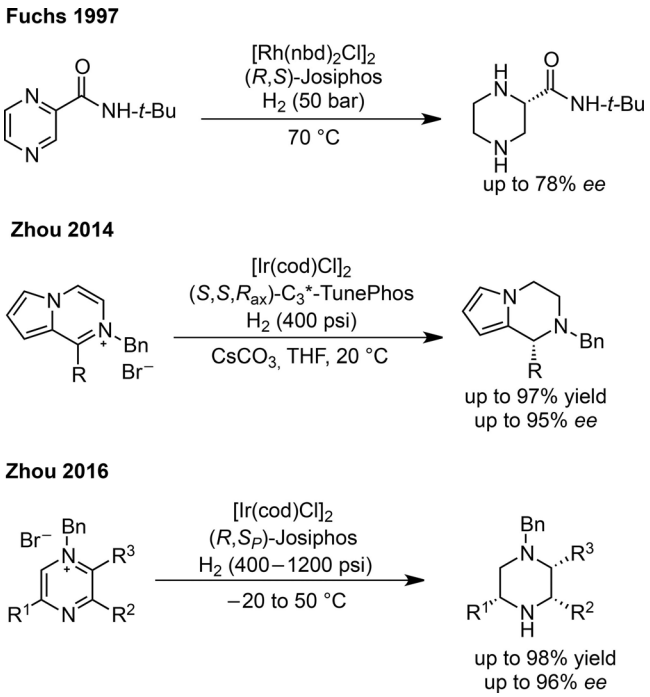


Scheme 1. Asymmetric hydrogenation of pyrazines reported so far.

eroaromatic compounds, the use of the HX salt formation of *N*-heteroaromatic compounds as substrates dramatically improved both the catalytic reactivity and the enantioselectivity. In this communication, we report that dinuclear chloride-bridged iridium(III) complexes **1a–g** (Figure 2) worked as catalysts for the asymmetric hydrogenation of 2-tosylamido-5-substituted pyrazines upon combination with stoichiometric amounts of the HBr salt of *N*,*N*-dimethylaniline as an additive, producing the corresponding chiral amidinated tetrahydropyrazines in high yield and high enantioselectivity, which were versatile precursors for chiral piperazine derivatives.

We initiated the asymmetric hydrogenation of 4-methyl-*N*-(5-phenylpyrazin-2-yl)benzenesulfonamide (**2a**) in 1,4-dioxane under hydrogen gas (30 bar) using (*S*)-**1a**, which resulted in very low catalytic activity (Table 1, entry 1). To improve the catalytic performance, salt formation of *N*-heteroaromatic compounds with Brønsted acids was strategically applied to trap the amine products that strongly coordinated

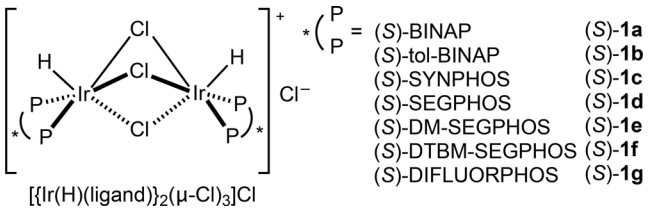
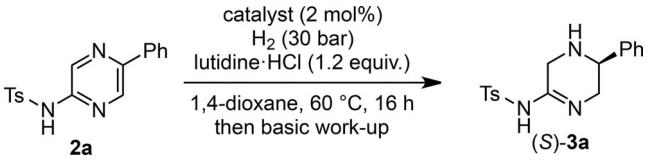


Figure 2. Dinuclear iridium(III) complexes used as catalysts.

Table 1. Screening of catalysts.



Entry	Catalyst	Yield [%][a]	*ee* [%][b]
1[c]	(*S*)-**1a**	23	47
2	(*S*)-**1a**	55	73
3	(*S*)-**1b**	34	55
4	(*S*)-**1c**	57	72
5	(*S*)-**1d**	53	70
6	(*S*)-**1e**	7	4
7	(*S*)-**1f**	trace	not determined
8	(*S*)-**1g**	43	83

[a] Determined by ^{1}H NMR analysis using triphenylmethane as an internal standard.
[b] Determined by HPLC analysis.
[c] Reaction was performed without lutidinium chloride.

with the iridium center. In fact, we had successfully applied such a salt formation strategy to reduce isoquinolinium salts,[16d,e] quinazolinium salts,[9] and pyridinium salts[16c] by adding stoichiometric amounts of lutidinium chloride as a source of HCl to trap the hydrogenated product **3a** *in situ*,[17] because **2a** did not produce its HCl salt due to its low basicity and lutidine was not hydrogenated under the catalytic conditions.[18] Thus, we conducted the asymmetric hydrogenation of **2a** in the presence of lutidinium chloride (1.2 equiv.) to give the product (*S*)-**3a** in 55% yield and 73% *ee* (entry 2). In the presence of lutidinium chloride (1.2 equiv.), we screened for the best catalyst, and the results are summarized in Table 1. Iridium complex (*S*)-**1b** bearing (*S*)-tol-BINAP showed less activity and low enantioselectivity (entry 3), while iridium complexes (*S*)-**1c** and (*S*)-**1d** bearing (*S*)-SYNPHOS and (*S*)-SEGPHOS, respectively, afforded (*S*)-**3a** in almost the same yield (53–57%) and with enantioselectivity (70–72%) (entries 4 and 5). When complexes (*S*)-**1e** and (*S*)-**1f** with much bulkier ligands were used as catalysts, hydrogenation did not proceed smoothly (entries 6 and 7). Finally, complex (*S*)-**1g** increased enantioselectivity (83%) although with a low yield (43%) of (*S*)-**3a**, and thus (*S*)-**1g** was selected as the best catalyst in terms of high enantioselectivity (entry 8).

With the best iridium catalyst in hand, we next examined salt additives, and the results are shown in Table 2. Among the salts of lutidine, such as lutidinium chloride, bromide, iodide, pentafluorobenzoate, and tosylate, the HBr salt of lutidine gave (*S*)-**3a** with the highest enantioselectivity (entries 1–5), and then we searched for various HBr salts of amines. Using 2,6-(*t*-Bu)$_2$pyridine as the bulky base, enantioselectivi-

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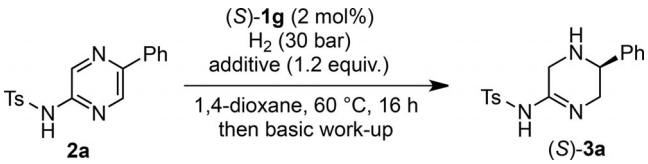
Table 2. Screening of additives.

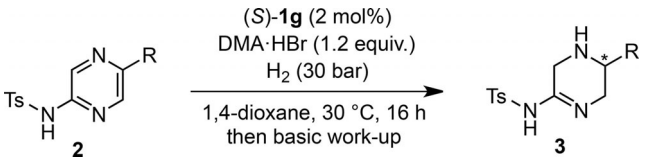


Entry	Additive	Yield [%][a]	*ee* [%][b]
1	lutidine·HCl	43	83
2	lutidine·HBr	63	88
3	lutidine·HI	80	83
4	lutidine·C_6F_5COOH	3	43
5	lutidine·TsOH	20	80
6	2,6-(*t*-Bu)$_2$pyridine·HBr	95	66
7	aniline·HBr	92	90
8	*p*-MeO-aniline·HBr	52	85
9	*p*-CF_3-aniline·HBr	98	75
10	*N*-methylaniline·HBr	97	88
11	*N*,*N*-dimethylaniline·HBr	>99	88
12[c]	*N*,*N*-dimethylaniline·HBr	>99 (98)[d]	93
13[c]	*N*,*N*-dimethylaniline·HCl	18	88
14[c]	*N*,*N*-dimethylaniline·HI	86	86

[a] Determined by ^{1}H NMR analysis using triphenylmethane as an internal standard.
[b] Determined by HPLC analysis.
[c] Reaction was conducted at 30 °C.
[d] Isolated yield.

ty was decreased to 66%, while (*S*)-**3a** was obtained in 95% yield (entry 6). When anilinium bromide was used as an additive, both the yield and enantioselectivity were increased in comparison with those of the reaction with lutidinium bromide, probably due to an interaction of amines and iridium metal center (entry 7).[16b,19] The electron-donating or electron-withdrawing substituent on aniline, however, led to a decrease in the enantioselectivity (entries 8 and 9). The addition of *N*-methylanilinium bromide and *N*,*N*-dimethylanilinium bromide in the reaction mixture improved the yield of the (*S*)-**3a** to 97% and >99%, respectively, with high enantioselectivity (entries 10 and 11). We performed an asymmetric hydrogenation of **2a** at 30 °C with *N*,*N*-dimethylanilinium bromide, and (*S*)-**3a** was isolated in 98% yield and 93% *ee* (entry 12). Finally, we further examined the halide effects by testing *N*,*N*-dimethylanilinium chloride and *N*,*N*-dimethylanilinium iodide, which resulted in lower yield and enantioselectivity (entries 13 and 14). Thus, it was rationalized that counter anions differentiated enantioselectivity due to the six-membered transition state involving the counter anion and N–H proton of the substrate salt.[15e] We therefore decided that the optimized conditions required 2 mol% of (*S*)-**1d** and 1.2 equivalents of *N*,*N*-dimethylanilinium bromide in 1,4-dioxane under hydrogen gas (30 bar) at 30 °C for 16 h.

Table 3. Scope and limitations.



Entry	R		Yield [%][a]	*ee* [%][b]
1	*p*-$MeOC_6H_4$	**2b**	98	92 (+)
2	*p*-$CF_3C_6H_4$	**2c**	76	78 (+)
3	*p*-$CO_2MeC_6H_4$	**2d**	91	91 (+)
4	*m*-$MeOC_6H_4$	**2e**	98	90 (+)
5	*m*-$CF_3C_6H_4$	**2f**	76	82 (+)
6	*o*-MeC_6H_4	**2g**	98	79 (+)
7	cyclopentyl	**2h**	96	86 (*S*)
8	*n*-hexyl	**2i**	94	84 (+)

[a] Isolated yield.
[b] Determined by HPLC analysis.
DMA = *N*,*N*-dimethylaniline

We applied the best conditions for various substrates (Table 3). Asymmetric hydrogenation of *p*-methoxy derivative **2b** quantitatively yielded (+)-**3b** with high enantioselectivity (92% *ee*) (entry 1), whereas introduction of an electron-withdrawing group such as CF_3 at the *p*-position decreased both the yield and enantioselectivity (entry 2). The ester group of **2d** remained intact under the reduction to give (+)-**3d** in 91% yield and 91% *ee* (entry 3). *m*-Methoxy-substituted substrate **2e** was hydrogenated smoothly to give (+)-**3e** in 90% *ee* (entry 4); however, asymmetric hydrogenation of *m*-trifluoromethyl-substituted substrate **2f** afforded only a moderate yield and enantioselectivity as well as that of **2c** (entry 5). A methyl group at the *m*-position decreased enantioselectivity due to steric hindrance (entry 6). Alkyl-substituted pyrazines were the competent substrates to afford the corresponding reductants, (*S*)-**3h** and (+)-**3i**, in high yield with moderately high enantioselectivity (entries 7 and 8). On the other hand, asymmetric hydrogenation of 2-tosylamido-6-phenylpyrazine did not proceed under the same conditions,[20] probably due to the tight coordination of the substrate to the iridium center since the substrate had no substitution next to the nitrogen atom at 4-position.[16g]

Scheme 2 shows the rational derivatization of (*S*)-**3a**. Hydration of (*S*)-**3a** with saturated K_2CO_3 aqueous solution under 60 °C converted the tosylamide group to a carbonyl group to afford (*S*)-**4a** in 91% yield with 92% *ee*. Reduction of (*S*)-**3a** with $LiAlH_4$ in THF followed by treatment with Boc_2O gave *tert*-butyl (*S*)-3-phenylpiperazine-1-carboxylate [(*S*)-**5a**] in 80% yield without loss of enantioselectivity.

To gain insights into the reaction pathway, deuteration of **2a** was conducted with deuterium gas (8 bar) and deuterium bromide salt as the deuterium sources

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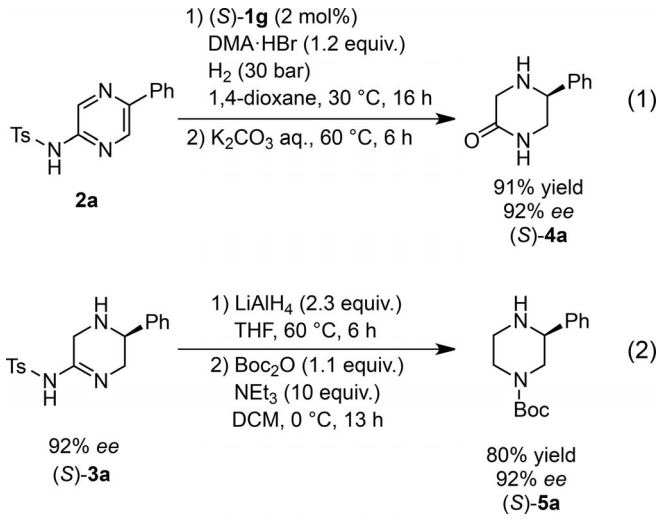
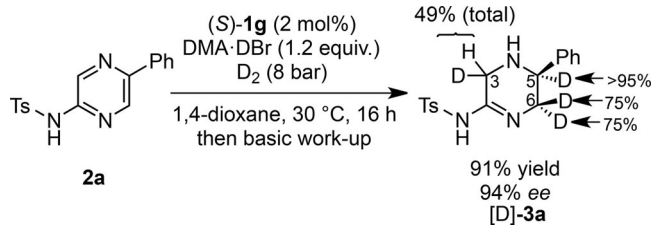


Scheme 2. Preparation of (*S*)-5-phenylpiperazin-2-one [(*S*)-**4a**] and *tert*-butyl (*S*)-3-phenylpiperazine-1-carboxylate [(*S*)-**5a**].



Scheme 3. Deuterium labeling experiment.

(Scheme 3). The distribution of deuterium in the deuterated product ([D]-**3a**) was determined by ^{1}H NMR, which revealed that 49%, >95%, and 75% of the deuterium was incorporated at the C-3, C-5, and C-6 positions, respectively. Based on these results, a plausible reaction pathway is proposed in Figure 3. Possible tautomerization between sulfonamide **2** and sulfonimide **I** was considered to promote dearomatization of the starting material.[21,22] After an initial reduction at the C-3=N-4 bond, amine **II** was trapped by *N*,*N*-dimethylanilinium bromide to give bromide salt **III** as an intermediate. According to the deuterium labeling experiment, an original hydrogen atom at the C-6 position was replaced with deuterium, suggesting tautomerization between enaminium **III** and iminium **IV**. Additionally, because of the equal deuterium distribution at both hydrogens of the methylene at the C-6 position, a second reduction proceeded at the N-4=C-5 bond of iminium **IV** to afford **3** as the resulting product.

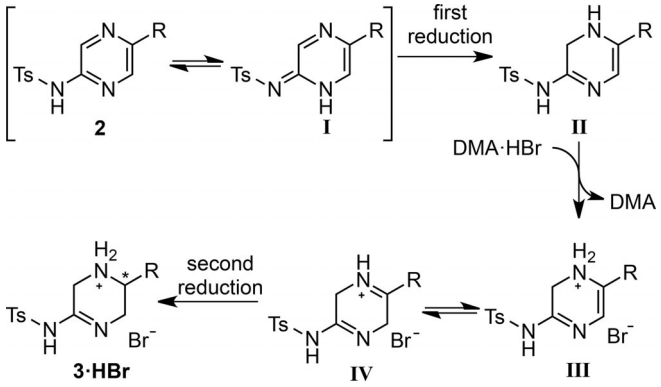


Figure 3. Possible reaction pathway.

In summary, tosylamide-substituted pyrazines were hydrogenated using dinuclear iridium(III) complexes as catalysts to afford the corresponding chiral tetrahydropyrazines bearing the amidine skeleton in high yield and with high enantioselectivity. Additionally, we demonstrated that the hydrogenated product, (*S*)-**3a**, was readily transformed to the corresponding chiral piperazinone and piperazine while maintaining enantiopurity.

Experimental Section

General Procedure for Ir-Catalyzed Asymmetric Hydrogenation of Pyrazine 2

Iridium complexes (2.4 μmol, 2.0 mol%), DMA·HBr (0.144 mmol, 1.2 equiv.), and 4-methyl-*N*-(5-phenylpyrazin-2-yl)benzenesulfonamide (**2a**) or its derivatives **2b**–**i** (0.12 mmol) were added to a glass tube in a reactor and the tube was charged with argon. Dry 1,4-dioxane (3 mL) was added to the glass tube in the reactor and charged with H_2, and the pressure was increased to the desired pressure. The reaction mixture was stirred for 16 h at 30 °C. After release of H_2, the reaction mixture was poured into a saturated aqueous solution of $NaHCO_3$ and extracted with DCM. The organic layer was dried over Na_2SO_4. The filtrate was concentrated under vacuum, and the residue was purified by column chromatography on silica gel (hexane/EtOAc = 50/50 to EtOAc) to afford the desired products.

Preparation of pyrazine **2**, general procedure for synthesizing **4a** and **5a**, full characterization data and copies of relevant spectra of all new products, and X-ray crystallographic analysis data of **3h**[23] are provided in the Supporting Information.

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Iridium-Catalyzed Asymmetric Hydrogenation of Tosylamido-Substituted Pyrazines for Constructing Chiral Tetrahydropyrazines with an Amidine Skelton

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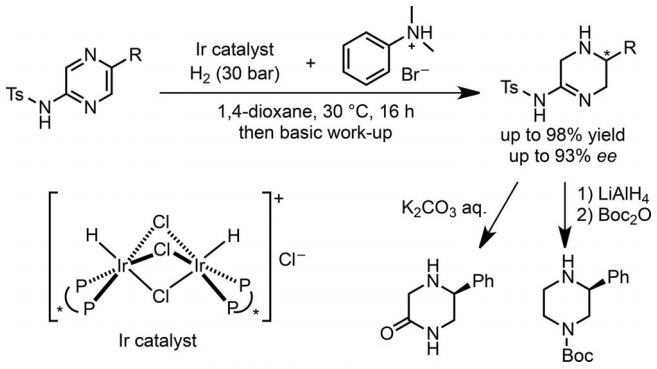
Kosuke Higashida, Haruki Nagae, Kazushi Mashima*

7



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