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Advanced Synthesis & Catalysis

Asymmetric Hydrogenation of 3-Amido-2-arylpyridinium Salts by Triply Chloride-Bridged Dinuclear Iridium Complexes Bearing Enantiopure Diphosphine Ligands: Synthesis of Neurokinin-1 Receptor Antagonist Derivatives

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Abstract: We describe a most straightforward synthetic method for preparing neurokinin-1 (NK1) receptor antagonist derivatives by asymmetric hydrogenation of 3-amido-2-arylpyridinium salts using dinuclear iridium complexes with enantiopure diphosphine ligands, affording the corresponding chiral piperidines in high *cis*-diastereoselectivity (>95:5) and moderately high enantioselectivity (up to 86%). Deprotection treatments afforded the NK-1 receptor antagonist (+)-CP-99,994 (83% *ee*). In addition, we observed unique additive effects of 10-camphorsulfonic acid in the asymmetric hydrogenation of 3-amido-2-arylpyridinium salts.

Keywords: asymmetric catalysis; hydrogenation; iridium; nitrogen heterocycles

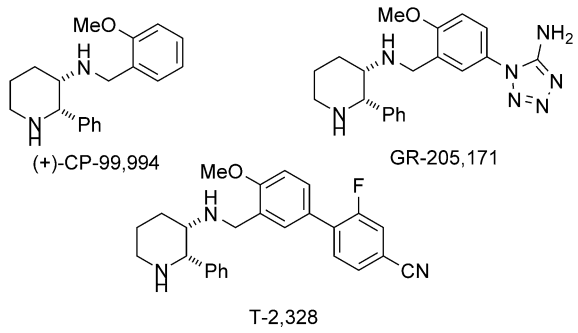
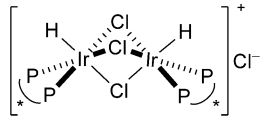


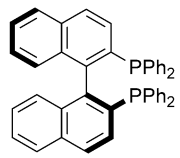
Figure 1. Antagonists of neurokinin-1 (NK1) substance P receptor.

Optically active piperidines are highly important molecular skeletons abundant in natural alkaloids and biologically active compounds, and are key intermediates for synthesizing drugs and fragrances. Among them, 3-amino-2-phenylpiperidine and its derivatives have attracted special interest due to their strong biological relevance as non-peptide antagonists of neurokinin-1 (NK-1) substance P receptors, such as (+)-(2*S*,3*S*)-CP-99,994, (+)-(2*S*,3*S*)-GR-205,171, and (+)-(2*S*,3*S*)-T-2,328, as shown in Figure 1.[1] From a synthetic point of view, chiral pool synthesis[1b,2] and diastereoselective reactions[3] for constructing the stereochemistry of the C-2 and C-3 positions of chiral piperidine derivatives have been investigated, but these synthetic methodologies require multistep synthesis after constructing the stereogenic centers.[4] Thus, asymmetric hydrogenation of 2-aryl-3-aminopyridines is considered the most simple and atom economical method for preparing chiral 2-aryl-3-aminopiperidines; however, the aromatic nature and strong coordination ability of pyridine and piperidine derivatives has prevented the practical development of such an asymmetric hydrogenation of pyridines.[5–8] In fact, a strategy of modifying pyridines, i.e., *N*-iminopyridinium ylides[9] and *N*-benzylpyridinium salts,[10] is required to actuate substrates for asymmetric hydrogenation. We recently developed a protocol for the asymmetric hydrogenation of the hydrogen halide salts of multisubstituted pyridines using enantiopure dinuclear iridium complexes **1** (Figure 2) to furnish the corresponding chiral piperidines with high diastereoselectivity and enantioselectivity.[11] Soon after, Zhou et al. applied our synthetic method to the asymmetric hydrogenation of the HCl salts of trisubstituted pyridine.[12] In this communication, we report that the asymmetric hydrogenation of 3-amido-2-arylpyridinium salts catalyzed by enantiopure dinuclear iridium complexes **1** in the presence of additional organic acids afforded the corresponding 3-amido-2-arylpiperidines in high diastereoselectivity and very high enan-

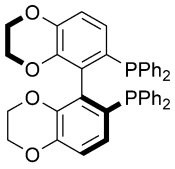


1: [{Ir(H)(L)}$_2$(μ-Cl)$_3$]Cl

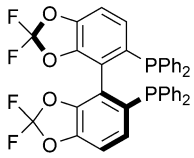
(*S*)-**1a**: L = (*S*)-BINAP
(*S*)-**1b**: L = (*S*)-SYNPHOS
(*S*)-**1c**: L = (*S*)-DIFLUORPHOS
(*S*)-**1d**: L = (*S*)-SEGPHOS
(*S*)-**1e**: L = (*S*)-DM-SEGPHOS



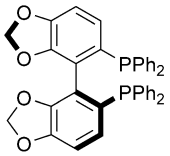
(*S*)-BINAP



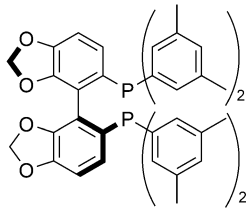
(*S*)-SYNPHOS



(*S*)-DIFLUORPHOS



(*S*)-SEGPHOS



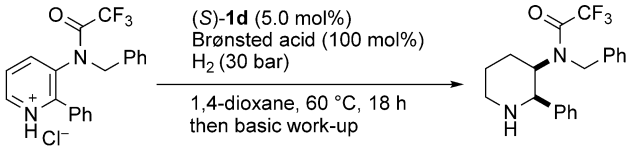
(*S*)-DM-SEGPHOS

Figure 2. Chloride-bridged dinuclear iridium complexes bearing enantiopure diphosphine ligands.

tioselectivity, providing a reliable access to the synthesis of NK1 receptor antagonist derivatives.

We selected 3-(*N*-benzyl-2,2,2-trifluoroacetamido)-2-phenylpyridin-1-ium chloride (**2a**·HCl) as a test substrate, and began by its hydrogenation under the conditions of [{Ir(H)[(*S*)-segphos]}$_2$(μ-Cl)$_3$]Cl [(*S*)-**1d**] in 1,4-dioxane at 60 °C for 18 h under H_2 (30 bar) to obtain the corresponding piperidine derivative (2*R*,3*R*)-**3a** in 60% yield with 82% *ee* after a basic work-up (Table 1, entry 1). After hydrogenation, we measured the ^{1}H NMR spectrum of the crude mixture to detect a trihyride dinuclear iridium complex (*S*)-**4d** (Figure 3), which was already reported to be catalytically inactive, but reactivated by the addition of suitable Brønsted acids.[13] Accordingly, we surveyed some Brønsted acids (100 mol% to the substrate) for adjusting the asymmetric hydrogenation of **2a**·HCl by (*S*)-**1d**, and the results are summarized in Table 1. Addition of (−)-10-camphorsulfonic acid [(−)-CSA] significantly increased the yield from 60% to 85% and the enantioselectivity from 82% to 84% (entry 1 *vs.* 2). On the other hand, (+)-CSA had smaller additive effects on the reactivity and enantioselectivity than (−)-CSA (entry 3). These match/mismatch effects of CSA suggested that CSA interacted with the catalytically active species. CSA was reported to activate indoles and qunolines prior to asymmetric hydrogenation catalyzed by palladium and iridium complexes.[14] Among the Brønsted acids examined, (−)-CSA was found to be superior to other additives, including TsOH·H_2O, acetic acid, adamantanecarboxylic acid (AdCOOH), benzoic acid, and pentafluorobenzoic acid (entries 4–8). In contrast to pyridinium salts,

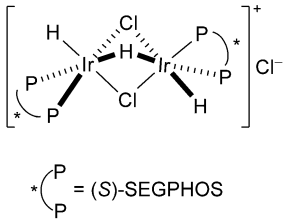
Table 1. Screening of Brønsted acids.[a,b]



2a·HCl (2*R*,3*R*)-**3a**

Entry	Brønsted acid	Yield[c] [%]	*ee*[d] [%]
1	none	60	82
2	(−)-CSA	85	84
3	(+)-CSA	66	80
4	TsOH·H_2O	99	81
5	CH_3COOH	37	83
6	AdCOOH	34	82
7	PhCOOH	23	82
8	C_6F_5COOH	54	81
9[e]	(−)-CSA	N.A.[f]	N.A.[f]

[a] *Reaction conditions:* mixture of **2a**·HCl (0.15 mmol), (*S*)-**1d** (7.5 μmol), Brønsted acid (0.15 mmol), and 1,4-dioxane (3 mL) under H_2 (30 bar) for 18 h.
[b] *cis*-(2*R*,3*R*)-**3a** was only observed in the ^{1}H NMR spectrum, and thus diastereoselectivity was estimated to be more than 95%.
[c] Determined by ^{1}H NMR analysis using phenanthrene as an internal standard.
[d] Determined by HPLC analysis of corresponding trifluoroacetamide.
[e] *Reaction conditions:* mixture of **2a** (0.15 mmol), (*S*)-**1d** (7.5 μmol), (−)-CSA (0.30 mmol), and 1,4-dioxane (3 mL) under H_2 (30 bar) was heated at 60 °C for 18 h.
[f] Complex mixture was obtained. ^{1}H NMR and HPLC analysis were not applicable.



= (*S*)-SEGPHOS

Figure 3. Structure of (*S*)-**4d**.

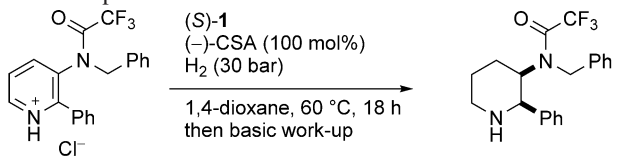
unionized pyridine **2a** was not hydrogenated at all to (2*R*,3*R*)-**3a** under the reaction conditions at 60 °C using 200 mol% of (−)-CSA, indicating that hydrogen chloride was crucially required for the reaction to proceed (entry 9).

Further optimization was carried out using various iridium complexes (*S*)-**1a**–(*S*)-**1e** using 100 mol% of (−)-CSA (Figure 2 and Table 2). Hydrogenation using (*S*)-**1a** [L=(*S*)-BINAP] and (*S*)-**1c** [L=(*S*)-DIFLUORPHOS] furnished (2*R*,3*R*)-**3a** in lower yield and lower enantioselectivity than when using (*S*)-**1d** (entries 1 and 3). (*S*)-**1b** [L=(*S*)-SYNPHOS] increased the yield to 88%; however, enantioselectivity was decreased to 72% (entry 2). Sterically-bulky (*S*)-**1e** [L=(*S*)-DM-SEGPHOS] did not improve the enantioselectivity (entry 5). Accordingly, we selected (*S*)-**1d** [L=(*S*)-SEGPHOS] as the optimal catalyst. In the 1.5 mmol scale reaction under the optimized conditions, (2*R*,3*R*)-**3a** was isolated in 70% with 85% *ee*.

A series of 3-amido-2-arylpyridinium salts was subjected to asymmetric hydrogenation under the optimized reaction conditions (Table 3). **2b**·HCl bearing an electron-donating group on the aryl group was hydrogenated with high enantioselectivity, although a higher temperature was required (entry 2). **2c**·HCl and **2d**·HCl bearing electron-withdrawing groups were also hydrogenated with moderate enantiomeric excess (entries 3 and 4). Hydrogenation of **2e**·HCl, whose aryl groups bear *ortho* substituents, led to lower reactivity because of the steric hindrance of the substituent in the *ortho* position (entry 5). A 2-thienyl group was tolerated under the hydrogenation conditions (entry 6). Salt **2g**·HCl bearing a 2-naphthyl group was also hydrogenated with moderate enantiomeric excess (entry 7), and salt **2h**·HCl without any substituent on the 2-position was not hydrogenated probably due to the tightly coordinating ability of substrate lacking a 2-aryl substituent (entry 8). Other protecting groups of the amino group were examined (entries 9 and 10): A benzoyl group improved the enantioselectivity (entry 9), while a 3,5-bis(trifluoromethyl)benzoyl group completely retarded the reaction (entry 10).

We applied this asymmetric hydrogenation as a key step in the synthesis of (+)-CP-99,994, a non-peptide antagonist of the NK1 receptor,[1b,c] to demonstrate the advantage of this synthetic protocol. The catalytic hydrogenation of **2a**·HCl using the combination of [{Ir(H)[(*R*)-segphos]}$_2$(μ-Cl)$_3$]Cl [(*R*)-**1d**] and

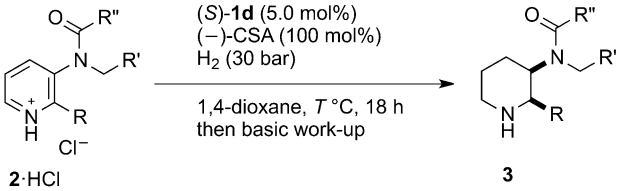
Table 2. Optimization of the reaction conditions.[a,b]



Entry	Ir cat.	Yield[c] [%]	*ee*[d] [%]
1	(*S*)-**1a**	60	66
2	(*S*)-**1b**	88	72
3	(*S*)-**1c**	77	73
4	(*S*)-**1d**	85 (70[e])	84
5	(*S*)-**1e**	75	66

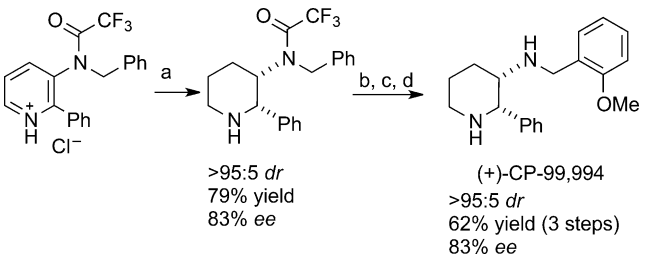
[a] *Reaction conditions:* A mixture of **2a**·HCl (0.15 mmol), (*S*)-**1** (7.5 μmol), (−)-CSA (0.15 mmol), and 1,4-dioxane (3 mL) under H_2 (30 bar) was heated at 60 °C for 18 h.
[b] *cis*-(2*R*,3*R*)-**3a** was only observed in the ^{1}H NMR spectrum, and thus diastereoselectivity was estimated to be more than 95%.
[c] Determined by the ^{1}H NMR analysis using phenanthrene as an internal standard.
[d] Determined by HPLC analysis of corresponding trifluoroacetamide.
[e] Isolated yield obtained in the 1.5 mmol scale reaction.

Table 3. Ir-catalyzed asymmetric hydrogenation of **2**·HCl.[a]



Entry	R/R'/R"		*T* [°C]	*dr*[b]	Yield[c] [%]	*ee*[d] [%]
1	Ph/Ph/CF_3	**2a**·HCl	60	>95:5	82	84 (−)
2	4-MeOC_6H_4/Ph/CF_3	**2b**·HCl	80	>95:5	88	85 (−)
3	4-$CF_3C_6H_4$/Ph/CF_3	**2c**·HCl	60	>95:5	75	70 (−)
4	4-CO_2Me-C_6H_4/Ph/CF_3	**2d**·HCl	60	>95:5	94	81 (−)
5	2-MeC_6H_4/Ph/CF_3	**2e**·HCl	80	>95:5	69	77 (−)
6	2-thienyl/Ph/CF_3	**2f**·HCl	80	>95:5	38	70 (+)
7	2-naphthyl/Ph/CF_3	**2g**·HCl	60	>95:5	73	76 (−)
8	H/Ph/CF_3	**2h**·HCl	80	N.A.[e]	trace	N.A.[f]
9	Ph/Ph/Ph	**2i**·HCl	60	>95:5[g]	75	86 (−)
10	Ph/Ph/3,5-bis(CF_3)C_6H_3	**2j**·HCl	60	N.A.[e]	trace	N.A.[f]

[a] *Reaction conditions:* A mixture of **2**·HCl (0.15 mmol), (*S*)-**1d** (7.5 μmol), (−)-CSA (0.15 mmol), and 1,4-dioxane (3 mL) under H_2 (30 bar) was heated for 18 h.
[b] Determined by ^{1}H NMR analysis.
[c] Isolated yield.
[d] Determined by HPLC analysis of corresponding trifluoroacetamide.
[e] A ^{1}H NMR analysis was not applicable.
[f] An HPLC analysis was not applicable.
[g] Determined by HPLC analysis.



Scheme 1. Synthetic application of Ir-catalyzed hydrogenation. *Reagents and conditions:* a) (*R*)-**1d** (5.0 mol%), (+)-CSA (100 mol%), 1,4-dioxane, 60 °C, H_2 (30 bar), 18 h, then basic work-up; b) K_2CO_3, MeOH/H_2O (3/1), 65 °C, 12 h; c) $Pd(OH)_2$/C, HCl (ether solution), MeOH, 50 °C, H_2 (15 bar), 18 h; d) *o*-anisaldehyde, $NaBH(OAc)_3$, *i*-PrOAc, room temperature, 3 h.

(+)-CSA, followed by a basic work-up gave (2*S*,3*S*)-**3a** in 79% yield with 83% *ee*, similar to the reaction using (*S*)-**1d** (Table 1, entry 2). After deprotection of the trifluoromethyl group and benzyl group, an *o*-methoxybenzyl group was attached to the 3-amino group without loss of enantiomeric purity, achieving the asymmetric synthesis of (+)-CP-99,994 (Scheme 1).

In summary, 3-amido-2-arylpyridinium salts were hydrogenated by chloride-bridged dinuclear iridium complexes to the corresponding 2-aryl-3-amidopiperidines in high diastereoselectivity and moderately high enantioselectivity. Current efforts are directed toward mechanistic studies on the effects of CSA on the asymmetric hydrogenation of pyridinium salts.

Experimental Section

General Procedure

Iridium complex (7.5 μmol, 5.0 mol%) and pyridinium salts (0.15 mmol, 1.0 equiv.) were added to a glass tube in a stainless autoclave reactor and the tube was charged with argon. Dry 1,4-dioxane (3 mL) was added into the glass tube in the reactor from the inlet, and charged with H_2 and the pressure was increased to the desired pressure. The reaction mixture was stirred for the appropriate period of time. After release of H_2, the reaction mixture with an internal standard (phenanthrene) was poured into a saturated aqueous solution of $NaHCO_3$ and extracted with EtOAc. The organic layer was passed through $MgSO_4$ and eluted with EtOAc. The filtrate was concentrated under vacuum to provide a yellow oil. The NMR yield was determined by ^1H NMR analysis using phenanthrene as internal standard. Purification by column chromatography on silica gel (hexane/EtOAc = 70/30 to 50/50) afforded the product. $KMnO_4$ was used as a TLC stain for the detection of piperidines. Trifluoroacetylation was needed for determination of their enantiomeric excess. The NMR sample was cooled to 0 °C by using an ice bath. Then ten drops of Et_3N and five drops of trifluoroacetic anhydride were added to the reaction mixture at 0 °C. The reaction mixture was warmed to room temperature and stirred overnight. The reaction mixture was washed with 1 M aqueous solution of HCl and poured into a saturated aqueous solution of $NaHCO_3$. After filtration through a short plug of Na_2SO_4 and silica gel and eluted with EtOAc the filtrate was concentrated under vacuum to provide a yellowish brown oil, which was dissolved in HPLC-grade IPA and analyzed by HPLC.

Acknowledgements

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