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Asymmetric Hydrogenation of 2-Aryl-3-phthalimidopyridinium Salts: Synthesis of Piperidine Derivatives with Two Contiguous Stereocenters

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Cite This: https://dx.doi.org/10.1021/acs.orglett.0c03261 Read Online

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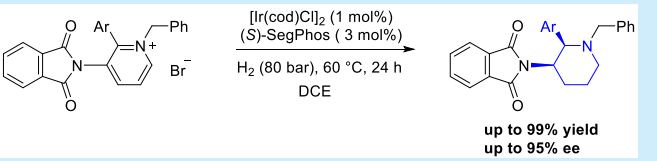
ABSTRACT: Asymmetric hydrogenation of 2-aryl-3-phthalimidopyridinium salts catalyzed by the Ir/SegPhos catalytic system was described, leading to the corresponding chiral piperidine derivatives bearing two contiguous chiral centers, with high levels of enantioselectivities and diastereoselectivities. A gram-scale experiment has demonstrated the utility of this approach. The phthaloyl group could be easily removed and then smoothly converted to key intermediate (+)-CP-99994 as one of the neurokinin 1 receptor antagonists.



Optically active piperidines are ubiquitous motifs present in a wide range of biologically active molecules, drugs, fragrances, and natural products, and they have attracted great interest for many research groups.[1] Among them, chiral 3-amino-2-arylpiperidines containing two contiguous centers as structural moieties featuring neurokinin 1 (NK-1) receptor antagonists have received much attention, such as (+)-CP-99994,[2] Vofopitant,[3] (+)-CP-122721,[4] and benzoamide piperidine,[5] as shown in Figure 1. Therefore, several synthetic

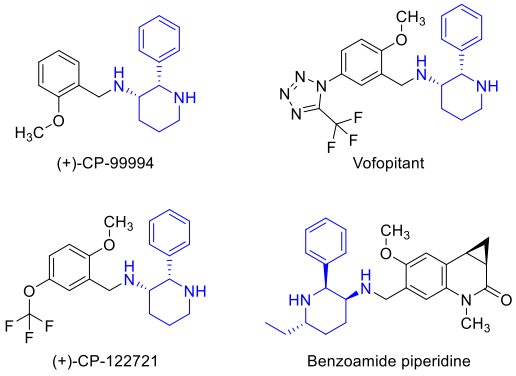


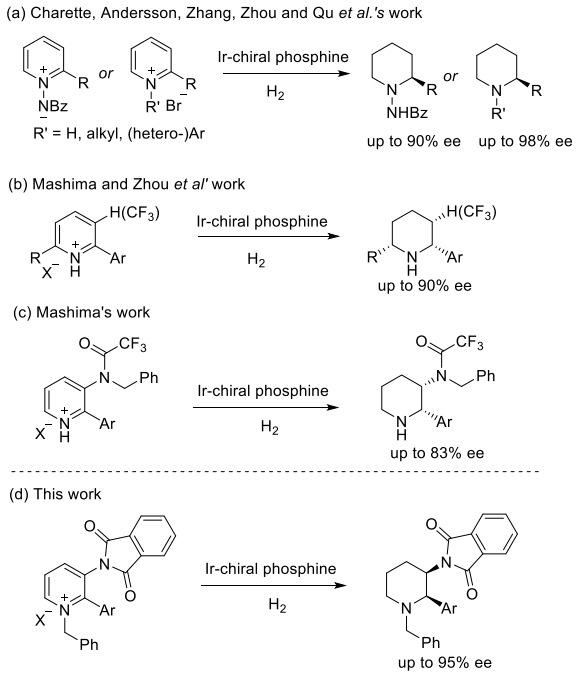
Figure 1. Neurokinin 1 receptor antagonists containing chiral piperidines.

strategies, including chiral synthon-based,[6] chiral auxiliary-mediated,[7] catalytic asymmetric synthesis,[8] and asymmetric hydrogenation (AH),[9] have been developed in preparing chiral 3-amino-2-arylpiperidines bearing two contiguous centers. However, compared to the former three methods usually requiring multiple synthetic steps, asymmetric hydrogenation benefits from its straightforward and high enantiocontrol and efficiency.

Considering the advances toward asymmetric hydrogenation of pyridine derivatives, several approaches have been reported, such as direct hydrogenation by a transition metal,[10] organocatalytic transfer hydrogenation,[11] and transition-metal-catalyzed asymmetric hydrogenation of activated pyridine derivatives.[12] The latter was one of the most effective strategies. Therefore, in 2004, Charette and co-workers have been successfully demonstrated by Ir/N,P ligand catalyzed asymmetric hydrogenation of *N*-benzoylpyridinium ylides to access chiral piperidine derivatives with high enantioselectivities (up to 90% ee).[13a] Later, Andersson et al. reported the same activated protocol in asymmetric hydrogenation of 2-alkyl-substituted *N*-iminopyridium ylides as well as furnishing the chiral piperidines up to 90% ee.[13b] Subsequently, an effective approach to access chiral piperidine derivatives with higher enantioselectivities (up to 98% ee) was described and developed by Zhou,[14] Zhang,[15] and Qu's[16] research groups utilizing Ir-diphosphine-catalyzed asymmetric hydrogenation of *N*-alkylpyridinium salts (Scheme 1a). In addition, Mashima and Zhou reported another strategy for the asymmetric hydrogenation of Brønsted acid activated multisubstituted pyridines using enantiopure binuclear iridium complexes, delivering the corresponding chiral piperidines with high diastereoselectivities and enantioselectivities (up to 90% ee) (Scheme 1b).[17] Soon after, Mashima developed a new route to the synthesis of neurokinin 1 receptor antagonists bearing the key structure skeleton of 2-aryl-3-amino piperidines through

Received: September 28, 2020

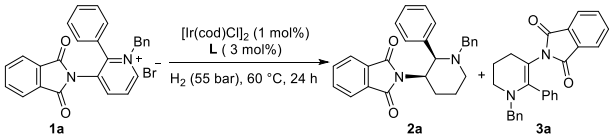
Scheme 1. Recent Advance in AH of 2-Substituted Pyridinium Salts



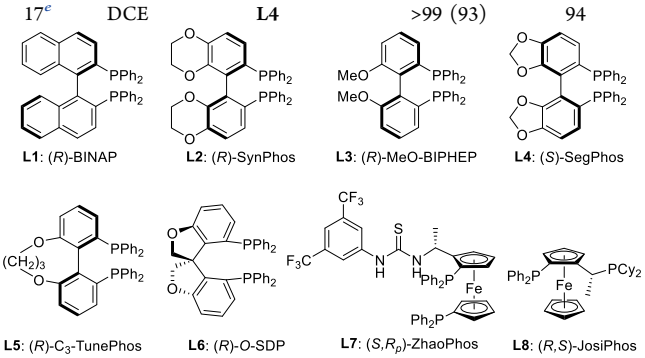
asymmetric hydrogenation of organic acid pyridinium salts with high diastereoselectivities and good enantioselectivities (up to 83% ee) (Scheme 1c).[9] Here, we reported a new type of 2-aryl-3-phthalimidopyridinium salts through Ir-diphosphine-catalyzed asymmetric hydrogenation to provide chiral 2-aryl-3-imidylpiperidine derivatives with high levels of diastereoselectivities and enantioselectivities (Scheme 1d).

We began our investigation with *N*-benzyl-2-phenyl-3-pyridinium salt **1a**, which was conveniently prepared by Suzuki coupling of 2-chloro-3-aminopyridine and phenyl boronic acid, then the amino group was protected by phthalic acid, followed by treatment with benzyl bromide. The initial asymmetric hydrogenation experiment was carried out by using **1a** as a standard substrate in 1,2-dichloroethane (DCE) at 60 °C for 24 h under H_2 (55 bar) in the presence of catalyst $[Ir(cod)Cl]_2$ (1 mol %) and (*R*)-BINAP (3 mol %) formed in situ, followed by a basic workup, affording the corresponding chiral piperidine derivative **2a** bearing two contiguous chiral centers with high levels of diastereoselectivity (>99:1) and enantioselectivity (90% ee) (Table 1, entry 1). Subsequently, to improve the enantioselectivity, we attempted to explore the effects of a series of chiral diphosphine ligands, which are commercially available or developed in our group; (*R*)-SynPhos gives 91% ee (Table 1, entry 2) and (*R*)-MeO-BIPHEP provides 92% ee (Table 1, entry 3). Surprisingly, the same high enantiomeric excess (94% ee) was obtained by using (*S*)-SegPhos and (*S*)-C_3-TunePhos[18] (Table 1, entries 4 and 5). However, medium enantioselectivities were attained for (*R*)-*O*-SDP[19] and (S,R_p)-ZhaoPhos,[20] respectively, of 69% and 45% ee (Table 1, entries 6 and 7). Additionally, low conversion was given for (*R,S*)-JosiPhos, and the ee of the trace product could not be determined (Table 1, entry 8). Considering (*S*)-SegPhos is commercially available, we selected it as the optimum ligand for further optimization. In a survey of dichloromethane and THF as solvent, full conversions were observed and the enantioselectivities slightly decreased to 92% ee and 87% ee,

Table 1. Optimization of the Reaction Conditions[a]



entry	solvent	L	conv (yield)[b] (%)	ee of **2a**[c] (%)
1	DCE	**L1**	>99	90
2	DCE	**L2**	>99	91
3	DCE	**L3**	>99	92
4	DCE	**L4**	>99 (86)	94
5	DCE	**L5**	>99	94
6	DCE	**L6**	>99	69
7	DCE	**L7**	>99	45
8	DCE	**L8**	20	*d*
9	DCM	**L4**	>99	92
10	THF	**L4**	>99	87
11	EtOAc	**L4**	88	52
12	toluene	**L4**	80	83
13	acetone	**L4**	90	70
14	CH_3CN	**L4**	50	90
15	1,4-dioxane	**L4**	95	82
16	MeOH	**L4**	90	*d*
17[e]	DCE	**L4**	>99 (93)	94



[a]Reaction conditions: **1a** (0.30 mmol), $[Ir(COD)Cl]_2$ (1.0 mol %), L (3.0 mol %); H_2 (55 bar), solvent (1.5 mL), 60 °C, 24 h. [b]Determined by ^1H NMR or HPLC area% at 210 nm; isolated yield was in parentheses. [c]Determined by chiral HPLC. [d]No product was detected. [e]DCE (3 mL) was used, H_2 (80 bar), with low ratio of byproducts.

respectively (Table 1, entries 9 and 10). The investigation of EtOAc, toluene, acetone, CH_3CN, and 1,4-dioxane proceeded with 50−95% conversions and moderate to good enantioselectivities (52−90%) (Table 1, entries 11−15). When protic solvent methanol was used, we only observed byproduct **3a** (Table 1, entry 16). Among the above results, we selected DCE as the most favorable solvent for further exploration. To reduce the byproduct, we removed the trace moisture on an autoclave, reduced the reaction concentration (0.1 M), and increased the hydrogen gas pressure (80 bar), and the target product **2a** was gained with a higher isolated yield (93%) without erosion of the enantiomeric excess. In addition, the absolute configuration of **2a** was determined by X-ray crystallographic analysis (CCDC no. 2013289).

To explore the usefulness of the Ir/(*S*)-SegPhos catalytic system, a wide range of 2-aryl-3-phathalimidopyridinium salts **1** were prepared and evaluated under the optimized conditions. Substrates **1b**, **1c**, **1d**, **1e**, and **1f** bearing electron-donating substituents on the aromatic ring were hydrogenated with high enantioselectivities (92−95% ee) and good to high yields (78−

https://dx.doi.org/10.1021/acs.orglett.0c03261
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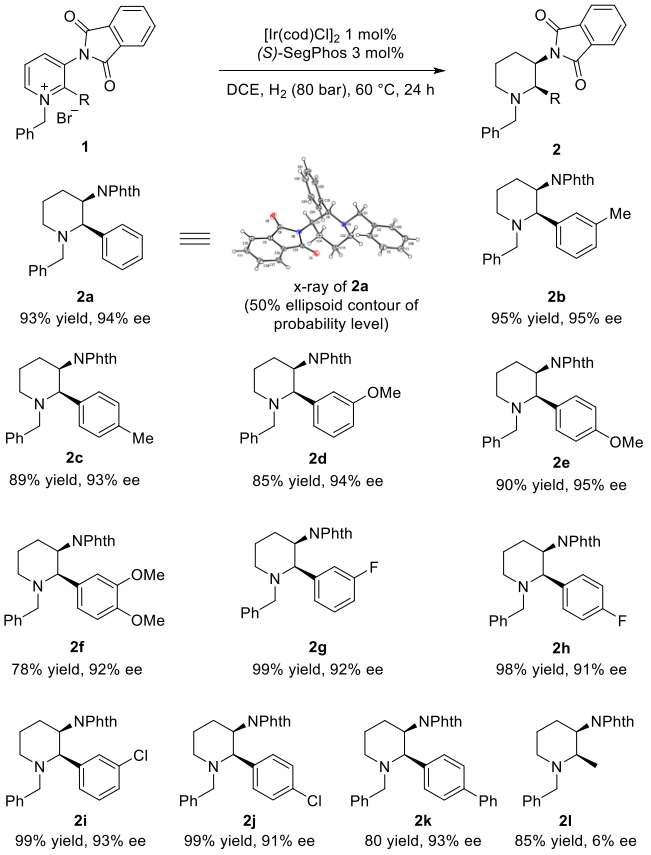
95%). However, substrates **1g**, **1h**, **1i**, and **1j** bearing electron-withdrawing substituents on the aromatic ring resulted in slight diminished enantioselectivities (91−93% ee), while provided with excellent yields (98−99%). For the substrate **1k** containing substituent phenyl at the *para*-position of aromatic group, the corresponding product **2k** was afforded with 80% yield and 93% enantiomeric excess. Only 6% ee was achieved for the hydrogenation of 2-alkyl-substituted pyridinium salt **1l** (Scheme 2).

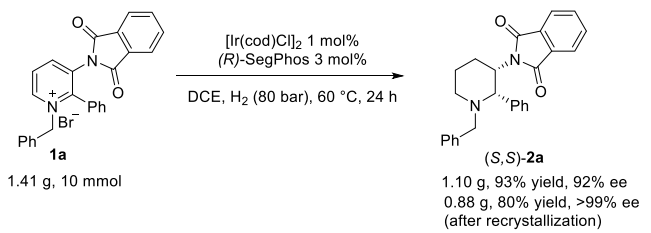
Scheme 2. Substrate Scope for Asymmetric Hydrogenation of 3-Phthalimido-2-arylpyridinium Salts



To further evaluate the practical utility, a gram scale hydrogenation of substrate **1a** catalyzed by Ir/(*R*)-SegPhos was carried out to produce the desired product (*S*,*S*)-**2a** with 93% yield and 92% ee, which was improved to >99% ee after a single crystallization (Scheme 3).

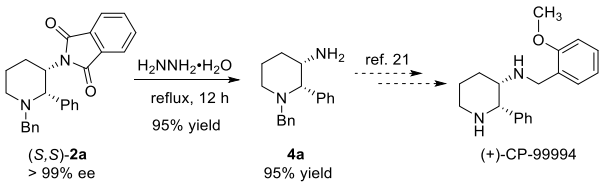
Furthermore, to broaden the application of our approach, we were devoted to synthesize of the formal structure of (+)-CP-99994. (*S*,*S*)-**2a** was successfully subjected to deprotection of

Scheme 3. Scale-up Experiment of Asymmetric Hydrogenation of 1a



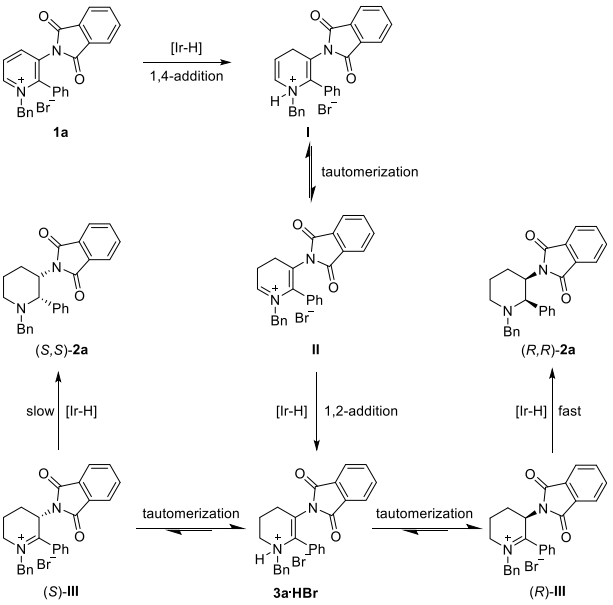
phthaloyl group using hydrazine hydrate, affording compound **4a** with 95% yield. Subsequently, removing the benzyl moiety, followed by reductive amination with the corresponding aldehyde gave (+)-CP-99994 according to the reported conditions[21] (Scheme 4).

Scheme 4. Synthetic Application for Constructing (+)-CP-99994



In addition, based on our previous work on the mechanism of asymmetric hydrogenation of 2-arylpyridinium salts with the Ir-MP^2-SEGPHOS catalyst,[22] we proposed a possible reaction route through an outer-sphere pathway involving sequential proton and hydride transfer via tautomerization (Scheme 5).

Scheme 5. Proposed Mechanism



1,4-Reduction of **1a** produces intermediate **I**, which is in equilibrium with intermediate **II**. 1,2-Reduction of intermediate **II** by an Ir−H species will generate hydrobromide byproduct **3a**, which aids in tautomerization of compounds (*S*)-**III** and (*R*)-**III**. The final product **2a** was obtained after diastereoselective reduction of intermediate **III**. The existence of intermediate **3a** was further verified by the fact that the asymmetric hydrogenation of hydrobromide of **3a** will also produce product **2a** in high yield under standard conditions.

In summary, we have developed a facile and effective approach through asymmetric hydrogenation of 3-phthalimido-2-arylpyridinium salts catalyzed by Ir/SegPhos to access chiral 3-amino 2-aryl piperidine derivatives with high diastereoselectivities and enantioselectivities, which were used as the structure motifs of NK-1 receptor antagonists. A gram scale-up synthesis of the chiral piperidine derivatives has demonstrated the practicality of this method. The synthetic

https://dx.doi.org/10.1021/acs.orglett.0c03261
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application for constructing (+)-CP-99994 further displays the utility of this strategy.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03261.

$^{1}H/^{13}C$ NMR data, spectra of all products, HRMS data of unknown products and crystallographic data (PDF)

Accession Codes

CCDC 2013289 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was sponsored by the Guangdong Provincial Key Laboratory of Catalysis (No. 2020B121201002), Shenzhen Nobel Prize Scientists Laboratory Project (C17213101), Southern University of Science and Technology (start-up fund), Shenzhen Science and Technology Innovation Committee (Nos. KQTD20150717103157174 and JSGG20170821140353405), National Natural Science Foundation of China (Nos. 21901107), and SZDRC Discipline Construction Program for financial support.

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