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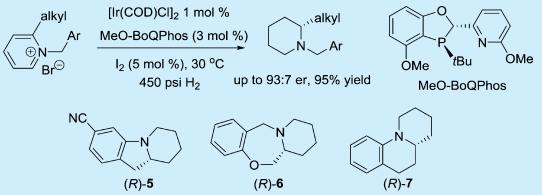
Synthesis of Enantioenriched 2-Alkyl Piperidine Derivatives through Asymmetric Reduction of Pyridinium Salts

Bo Qu,* Hari P. R. Mangunuru, Xudong Wei, Keith R. Fandrick, Jean-Nicolas Desrosiers, Joshua D. Sieber, Dmitry Kurouski, Nizar Haddad, Lalith P. Samankumara, Heewon Lee, Jolaine Savoie, Shengli Ma, Nelu Grinberg, Max Sarvestani, Nathan K. Yee, Jinhua J. Song, and Chris H. Senanayake

Chemical Development, Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, Connecticut 06877, United States

Supporting Information

ABSTRACT: An Ir-catalyzed enantioselective hydrogenation of 2-alkylpyridines has been developed using ligand MeO-BoQPhos. High levels of enantioselectivities up to 93:7 er were obtained. The resulting enantioenriched piperidines can be readily converted into biologically interesting molecules such as the fused tricyclic structures **5**, **6**, and **7** in 99:1 er, providing a novel, concise synthetic route to this family of chiral piperidine-containing compounds.



Chiral 2-alkyl piperidine is a ubiquitous motif found in a wide range of medicinally important compounds including many naturally occurring alkaloids (Figure 1).[1,2] 2-Alkyl piperidine-containing molecules have exhibited a broad spectrum of interesting biological activities such as potential analgetics,[3] antiamnestic agents,[4] and for the treatment of neurological diseases and psychiatric disorders.[5]

The reported synthetic strategies generally require long synthetic sequences to obtain the target chiral piperidines,[6] starting from the chiral pool, use of chiral auxiliaries, or through resolution of racemic mixtures. We are interested in synthesizing a series of chiral 2-alkylpiperidine derivatives and sought to access these molecules through an efficient and enantioselective approach. To this end, we envisioned installing the chiral center directly through asymmetric hydrogenation (AH) of 2-alkylpyridine derivatives. Substituted pyridines are readily available; the successful implementation of this protocol would provide an efficient atom-economical fashion for the preparation of enantiomerically enriched 2-alkyl piperidines.

Recent advances in asymmetric reduction of the heteroarenes have enabled a straightforward synthesis for enantioenriched heterocyclic compounds.[7] To facilitate the asymmetric reduction of pyridines, Charette and Legault first demonstrated an activation process for pyridine derivatives by forming *N*-acylimino-pyridinium ylides; high enantioselectivity was provided for 2-alkylpyridines.[8] Nevertheless, safety concerns[9] related to the use of amination reagents for the preparation of the requisite ylides prevent us from utilizing this elegant method on large scale.

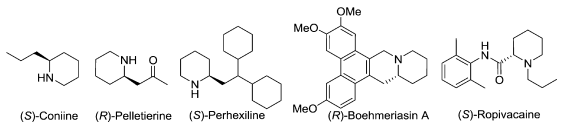
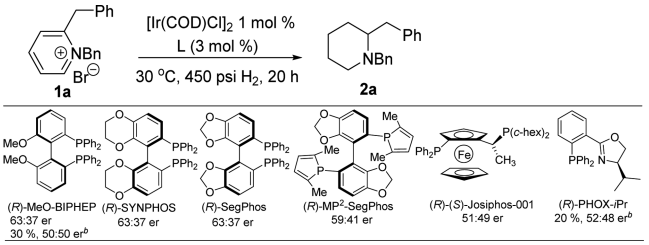


Figure 1. 2-Alkyl piperidine-containing alkaloids.

Scheme 1. Selected Known Ligands for AH of 1a[a]



[a]THF/MeOH 9:1, 100% conv to product unless specified, determined by HPLC area % at 220 nm. [b]In the presence of 5 mol % I_2, ratio of I_2/Ir = 2.5:1.

Zhou's[10] and Zhang's[11] groups then activated the pyridines by forming *N*-benzylpyridinium salts. A number of 2-aryl derived pyridines are reduced successfully with high enantioselectivities, but with limited application to 2-alkylpyridines. Herein, we report the development of an Ir-catalyzed enantioselective hydrogenation of 2-alkyl *N*-benzylpyridinium salts using BI *P,N* ligand MeO-BoQPhos, and its application toward the synthesis of the fused tricyclic piperidine-containing pharmacophores hexahydropyridoindole (*R*)-**5**, hexahydrobenzopyridooxazepine (*R*)-**6**, and benzoquinolizidine (*R*)-**7** in enantiomerically pure form.

Our investigation started with the readily accessible compound 2-benzyl-*N*-benzylpyridinium bromide salt **1a**. Commercially available chiral phosphine ligands were initially the focus under the conditions of 1 mol % $[Ir(COD)Cl]_2$, 30 °C, and 450 psi H_2 pressure (Scheme 1). Disappointing enantioselectivities resulted including Synphos[10] and MP^2-Segphos,[11] which are highly effective for 2-arylpyridinium salt reduction. Iodine is known to activate the iridium catalyst for catalytic hydrogenation reactions.[8,12] However, it was found that, for the reduction of **1a**

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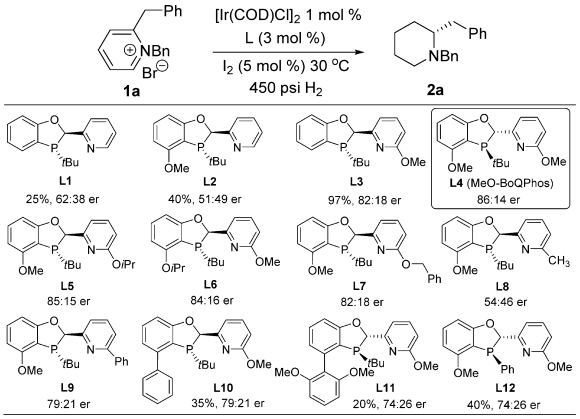
with bisphosphine ligands, the presence of iodine was detrimental to both reactivity and enantioselectivity.

We have recently introduced a family of new phosphorus ligands derived from a modular dihydrobenzooxaphosphole core and demonstrated their unique capability for a wide range of catalytic transformations.[13] In particular, the phosphorus-pyridine BoQPhos ligands have shown to reduce unfunctionalized alkenes enantioselectively with an iridium catalyst.[14] Since 2-alkylpyridines contain largely uncoordinating functionalities, we postulated these ligands could be also effective for the asymmetric reduction of pyridinium salts (Scheme 2). We first tested the unsubstituted ligand **L1** for hydrogenation of **1a** with $[Ir(COD)Cl]_2$ at 30 °C and 450 psi H_2 pressure; 25% conversion was observed. To enhance the reactivity, electron-donating alkoxy groups were incorporated into the ligand structure. Methoxy substitution on the left-hand side of the phenyl ring improved the conversion slightly to 40%, but again with no enantioselectivity (**L2**). On the other hand, ligand **L3** with a methoxy group on pyridyl generated the desired product **2a** in 97% conversion and an 82:18 er. The best enantioselectivity (86:14 er)[15] was achieved when methoxy groups were installed on both the phenyl and pyridyl rings as in (*S*,*S*)-**L4** (MeO-BoQPhos). Further fine-tuning of substitution on the pyridyl group did not significantly improve the selectivity (**L5** to **L9**). Aryl substitution on the phenyl group or phosphorus atom (**L10** to **L12**) decreased the reactivity.

Scheme 2. BoQPhos Ligands for AH of 1a[a]



[a]THF/MeOH 9:1, 20 h, 100% conv to **2a** unless specified, determined by HPLC area % at 220 nm.

We have previously observed that an iridacyclic complex is formed through Ir insertion to the C−H bond of the neighboring OMe group in the presence of a noncoordinating anion such as BAr_F (Scheme 3).[14] This complex is unreactive toward the asymmetric reduction of alkenes. In the presence of a strongly coordinating chloride, the anticipated neutral complex IrCl(MeO-BoQPhos)(COD) **3** was successfully isolated. The single crystal structure of **3**[16] clearly indicated an intact MeO group on pyridine in the molecule.

Complex **3** proved to be effective toward asymmetric hydrogenation of the pyridinium salt **1a** and was directly employed for solvent screening to eliminate the uncertainty of incomplete ligation in various solvents (Table 1). A variety of solvents and solvent mixtures were examined, with THF identified as optimal furnishing a 90:10 er (entry 3). This represents the highest enantioselectivity reported for 2-benzyl-*N*-benzylpyridinium salt **1a** compared to those obtained with bisphosphine ligands.[10,11]

Scheme 3. Structure of the Complex [IrCl(MeO-BoQPhos)(COD)] (3)

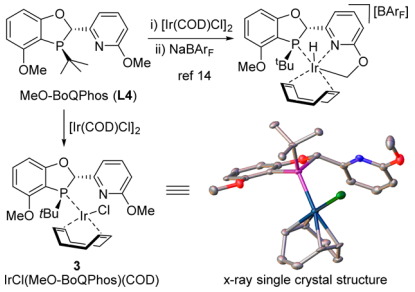
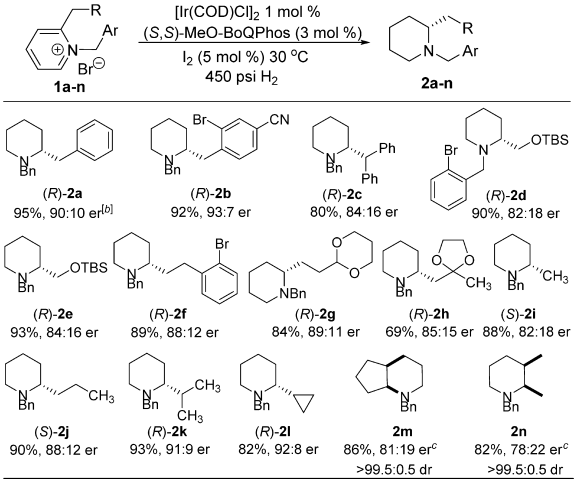


Table 1. Solvent Screening for AH of 1a Using Complex 3[a]

entry	solvent	**2a** (%)[b]	er
1	THF/MeOH (9:1)	100	86:14
2	THF/MeOH (3:1)	100	82:18
3[c]	**THF**	**100**	**90:10**
4	DCM	93	75:24
5	DCE	79	67:33
6	1,4-dioxane	92	80:20
7	toluene	92	82:18
8	toluene/DCM (1:1)	80	74:26
9	THF/*n*-BuOH (3:1)	100	82:18
10	acetone	99	52:48

[a]Reaction conditions: 30 mg of **1a**, 2 mol % **3**, 5 mol % I_2, 30 °C, 450 psi H_2 in 0.6 mL of solvent. [b]HPLC area % at 220 nm. [c]20 °C.

Scheme 4. AH of 2-Alkyl-*N*-benzylpyridinium Salts[a]



[a]Reaction conditions: pyridinium salt (0.5 g), 20 mL of THF, 5−24 h, isolation yield. [b]20 °C. [c]$[Ir(COD)Cl]_2$ 2 mol %, ligand 6 mol %, I_2 10 mol % at 10 °C and 600 psi H_2 for 24 h.

With the optimized conditions in hand, the substrate scope was then evaluated (Scheme 4). An enantiomeric ratio of 93:7 was observed for the piperidine **2b** with 2-bromo-4-cyano benzyl substitution. Most importantly, the catalyst system proved to be chemoselective at reducing the pyridine ring without affecting the reduction sensitive bromo and cyano groups. Hindered substrate 2-diphenylmethylpyridinium salt **1c** was reduced as well to produce an 84:16 er. The TBS protected 2-methanol pyridinium salt **1d** and **1e** are expected to be unfavorable substrates in terms of enantioselectivity; 82:18 er and 84:16 er were obtained, respectively. The catalyst is also effective for 2-alkylpyridinium

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salts containing long alkyl chains. *N*-Benzyl-2-phenethylpyridinium **1f** was reduced to the corresponding chiral piperidine **2f** with an 88:12 er. Pyridinium salts with acetal and ketal functionality on the alkyl group were reduced successfully to yield 89:11 er (**2g**) and 85:15 er (**2h**). 2-Methylpyridinium salt **1i** was reported to afford product **2i** in a 67:33 er upon hydrogenation using MP^2-Segphos as a ligand.[11] With Ir-MeO-BoQPhos, 2-methylpiperidine **2i** was obtained in a much improved 82:18 er. Similarly, 2-propylpiperidine **2j** and 2-isopropylpiperidine **2k** were obtained in 88:12 er and 91:9 er, respectively. A cyclopropyl substituent is tolerated to generate chiral piperidine **2l** in a 92:8 er.

Enantioselective reduction of the more challenging 2,3-disubstituted pyridinium salts including cyclic compound **1m** and acyclic compound **1n** was also evaluated. Presumably, complete hydrogenation proceeds through a tetrasubstituted enamine intermediate, which has been shown to be the most demanding substrate toward hydrogenation due to a high energy barrier and challenging facial differentiation.[17] The resulting fused bicyclic chiral piperidine would be an interesting structure that contains two embedded contiguous stereogenic centers.[18] To our delight, the asymmetric reduction of **1m** produced the enantioenriched **2m** in an exclusive *cis*-fashion with a 81:19 er and 86% yield. The acyclic 2,3-dimethylpiperidine **2n** was obtained in >99.5:0.5 dr and 78:22 er in 82% isolation yield.

Computational studies were conducted on the key enamine intermediate with (*S*,*S*)-**L4** to understand the enantioinduction process (Figure 2). All calculations were conducted with Gaussian 09[19] at the DFT level of theory with the B3LYP[20] and LANL2DZ basis set with ECP for iridium[21] and D95v for the remaining atoms.[22] A viable reaction pathway was found employing an outer-sphere dissociated mechanism[23] similar to the mechanism of iridium catalyzed asymmetric reduction of imines[24a] and quinolone derivatives.[24b] This pathway indicates that iodine activated the Ir(I) precatalyst; the resulting Ir(III) iodo complex is maintained as a neutral or charge balanced state throughout the two-step protonation and hydride delivery catalytic cycle. Although the rate-limiting step is the protonation (TS-1), the hydride delivery proceeds through a dissociative mechanism (TS-2) and thus the second transition state would dictate the facial selectivity of the process. Of the three potential hydrides on the iridium(III) intermediate, the one adjacent to the methoxypyridine residue of the ligand is sterically more accessible. The methoxy appendage of the pyridine orients the iminium substrate to expose the *si*-face for hydride delivery and generating the *R*-enantiomer of **2a**.

The resulting enantioenriched 2-alkyl piperidines can be readily converted into naturally occurring alkaloids including Coniine (from **2j**) and Pelletierine (from **2h**) and pharmaceutically important molecules such as chiral Desoxylpipradrol[25] (from **2c**). Furthermore, they were demonstrated in the syntheses of several enantiomerically pure fused tricyclic piperidine-containing molecules.

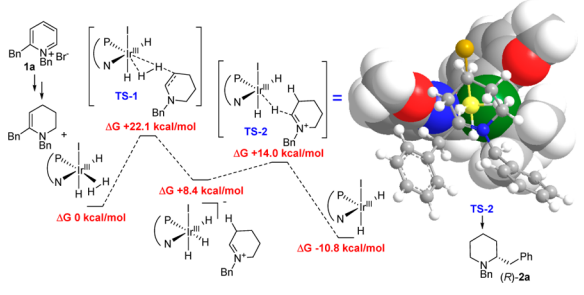
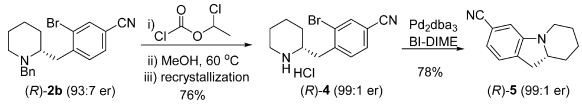


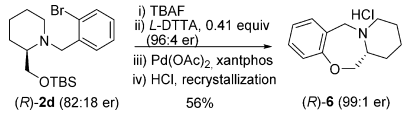
Figure 2. Outer-sphere dissociative catalytic cycle of the Ir-catalyzed reduction of enamine intermediate. DFT calculations: B3LYP/LANL2DZ, CPCM solvation model with THF. Thermal corrections: 298.15 K at 1 atm. Plot: 3D-Model of TS-2.

The reaction mixture of **2b** was subjected to debenzylation by treatment with α-chloroethyl chloroformate[26] in the presence of 0.2 equiv of $i\mathrm{Pr}_2\mathrm{NEt}$ in refluxing MeOH (Scheme 5). Recrystallization of the resulted HCl salt enriched the enantiomeric purity of **4—HCl** to 99:1 er. The deprotected chiral piperidine was isolated in 76% yield. An intramolecular Hartwig—Buchwald amination furnished (*R*)-**5** in 78% yield upon isolation. To our knowledge, this is the first enantioselective synthesis of hexahydropyridoindole derivatives.[27]

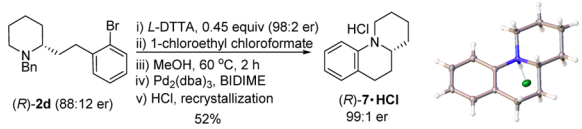
Scheme 5. Synthesis of Hexahydropyridoindole (*R*)-5



Scheme 6. Synthesis of hexahydrobenzopyridooxazepine (*R*)-6



Scheme 7. Synthesis of Tricyclic Benzoquinolizidine (*R*)-7



The *N*-benzyl fragment can also be utilized as an integral part of the molecule for further transformation (Scheme 6). Chiral enrichment on the corresponding alcohol from **2d** increased the enantiomeric purity to 96:4 er. Intramolecular ether formation and recrystallization of the HCl salt afforded the enantiomerically pure (*R*)-**6**[5,28] in 99:1 er.

Finally, a benzoquinolizidine derivative **7**[12d,29] was conveniently prepared from **2f** (Scheme 7). It was first subjected to chiral enrichment and then converted into compound (*R*)-**7** via debenzylation and an intramolecular amination (Scheme 7).

In summary, an Ir-catalyzed enantioselective hydrogenation of 2-alkyl-pyridinium salts has been developed using MeO-BoQPhos as the ligand. High levels of enantioselectivity up to 93:7 er were obtained, which represents an efficient and practical method for the preparation of enantioenriched piperidines. The resulting piperidines can be readily transformed into biologically interesting molecules such as fused tricyclic hexahydropyridoindole, benzoquinolizidine, and hexahydrobenzopyridooxazepine derivatives in 99:1 er, providing a concise and novel synthetic route to this family of chiral piperidine-containing compounds.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02401.

Experimental details and characterization data (PDF)

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AUTHOR INFORMATION

Corresponding Author

*E-mail: bo.qu@boehringer-ingelheim.com.

Notes

The authors declare no competing financial interest.

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(9) Compounds *o*-(2,4-dinitrophenyl)hydroxylamine and N-Boc-hydroxylamine show high energy decomposition at a relatively low onset temperature. Handling, shipment, and storage of these materials pose significant safety risks on large scales. See the Supporting Information for the Differential Scanning Calorimetry (DSC) plots.

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(15) The major enantiomer is (*R*)-configuration, derived from DFT calculation and the X-ray single crystal structure of (*R*)-**7**-HCl salt.

(16) CCDC-1477152 and CCDC-1478240 contain supplementary crystallographic data for compounds **3** and **7**, respectively. This material is free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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