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Synthesis of Chiral 2-Substituted 1,4-Benzoxazin-3-ones via Iridium-Catalyzed Enantioselective Hydrogenation of Benzoxazinones

Yu Nie, Jing Li, Jun Yan, Qianjia Yuan,* and Wanbin Zhang*

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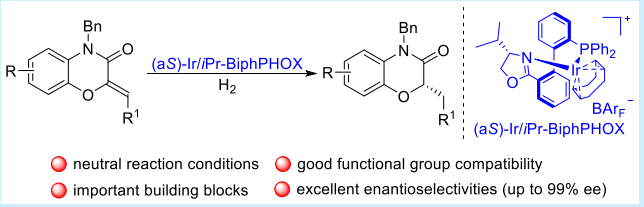
ABSTRACT: An efficient iridium-catalyzed enantioselective hydrogenation of 2-alkylidene 1,4-benzoxazin-3-ones using our developed *i*Pr-BiphPHOX as a ligand is reported. This method showed good functional group compatibility and delivered the corresponding reduced products in excellent yields (up to 99%) with excellent enantioselectivities (up to 99% ee). The reaction proceeded very well on a gram scale with low catalyst loadings (0.1 mol %), providing the product with no erosion in enantioselectivity. Additionally, three bioactive molecules can be easily obtained from the reduced products.



1,4-Benzoxazinones are core scaffolds in a variety of natural products and bioactive molecules as well as useful building blocks in organic synthesis (Figure 1).[1] Many synthetic

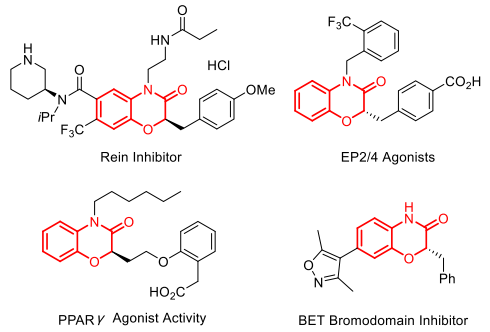
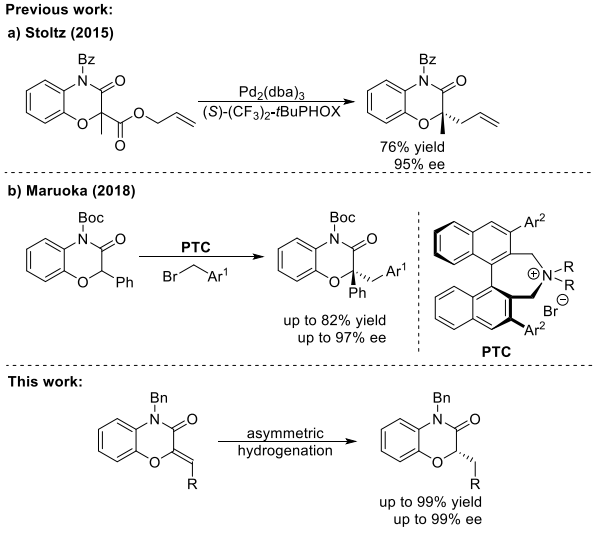


Figure 1. Examples of bioactive compounds bearing 1,4-benzoxazin-3-ones.

strategies have been reported for the construction of 1,4-benzoxain-3-ones;[2] however, most of the methods provide racemic mixtures,[2c−j] and the methods for the preparation of these chiral building blocks employ chiral starting materials and require multistep synthetic sequences.[2a,b] Hence, developing enantioselective catalytic strategies for the construction of enantiomerically enriched 1,4-benzoxazin-3-ones is of great importance; however, only a few examples of the construction of chiral 1,4-benzoxazin-3-ones via enantioselective catalytic reactions have been reported.[3] In 2015, Stoltz and coworkers synthesized 2,2-disubstituted 1,4-benzoxazin-3-ones via a palladium-catalyzed enantioselective allylic substitution reaction (Scheme 1a).[3a] In 2018, the Maruoka research group reported a phase-transfer-catalyzed enantioselective synthesis of 2,2-disubstituted 1,4-benzoxazin-3-ones (Scheme 1b).[3b] Therefore,

Scheme 1. Catalytic Enantioselective Synthesis of Chiral 2-Substituted 1,4-Benzoxazin-3-ones



the development of a concise method for the synthesis of such chiral compounds appears to be challenging but desirable.

Transition-metal-catalyzed enantioselective hydrogenation has gained much attention in academia, and great success has been achieved in industrial applications owing to its atom economy, excellent enantioselectivity, and simple operation for

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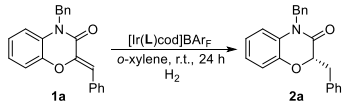
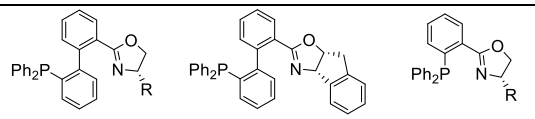
the construction of enantioenriched compounds.[4] Since the Pfaltz group's pioneering work,[5] iridium-catalyzed enantioselective hydrogenation has attracted much attention due to its excellent performance in the enantioselective reduction of different types of C═C bonds with/without functional groups. Our group has developed axis-unfixed biphenylphosphine-oxazoline ligands (**BiphPHOX**) that have shown excellent performance in several types of transition-metal-catalyzed enantioselective catalytic reactions,[6] especially for iridium-catalyzed enantioselective hydrogenations.[6a−f,h−l] Considering the importance of 1,4-benzoxazin-3-ones and to further explore our developed axis-unfixed biphenylphosphine-oxazoline ligands in the enantioselective hydrogenation reactions and the methods for the construction of chiral heterocycles,[7] herein we report an Ir/**BiphPHOX**-catalyzed enantioselective hydrogenation of 2-alkylidene 1,4-benzoxazin-3-ones for the preparation of chiral 2-substituted 1,4-benzoxazin-3-ones (Scheme 1). Our developed **BiphPHOX** ligands showed excellent performance in the iridium-catalyzed enantioselective reduction of four- and five-membered ring substrates bearing exocyclic C═C bonds but provided moderate enantiomeric ratios for the enantioselective reduction of six-membered rings bearing exocyclic C═C bonds.[6b,d] The development of an efficient enantioselective Ir/**BiphPHOX**-catalyzed hydrogenation of six-membered rings bearing exocyclic C═C bonds is desirable.

Optimization of the iridium-catalyzed enantioselective hydrogenation reaction was carried out using *N*-benzyl-substituted compound **1a** as the model substrate for six-membered rings bearing an exocyclic C═C bond (Table 1). On the basis of our previous reports,[6] the ligands **L1**−**L3** were tested under the enantioselective hydrogenation conditions. To our delight, the reaction proceeded very well and delivered the corresponding product **2a** with excellent enantioselectivities (entries 1−3). It should be noted that the substituent on the oxazoline ring of the ligand had no effect on the enantioselectivity of the reduced product. The PHOX ligands **L4** and **L5** were also tested in this reaction, and poor conversions and enantioselectivities were obtained (entries 4 and 5). Next, the solvent (DCE, toluene, and 1,4-dioxane) for the reaction was investigated, and the reduced products were all obtained with 96% ee (entries 6−8). The hydrogen pressure and reaction time were also examined (entries 9−11), both of which had an effect on the conversions of the reaction. When the hydrogen pressure was decreased to 30 bar, the reaction proceeded very well and gave the reduced product **2a** with 97% ee (entry 9). Finally, the protecting group on the nitrogen in the substrate was evaluated, and substrates bearing *N*-phenyl and *N*-methyl groups delivered their corresponding reduced products **2b** and **2c** with full conversions with 89 and 78% ee, respectively; however, the *N*-free substrate delivered a trace amount of product **2d**. On the basis of the above information, benzyl was selected as the nitrogen protecting group, and the optimized reaction conditions are shown in Table 1 (entry 9).

With the optimized reaction conditions in hand (Table 1, entry 9), the substrate scope was examined (Scheme 2). In general, the optimized reaction conditions showed excellent functional group compatibility. First, the substrates with different substituted R^2 groups were examined. When R^2 was a phenyl ring bearing different functional groups (electron-donating or electron-withdrawing) at the para or meta positions, all of the reduced products (**2a** and **2e**−**2o**) were obtained in excellent yields with excellent enantioselectivities; with a phenyl ring bearing a substituent at the ortho position, the reduced

Table 1. Screening of the Reaction Conditions[a]





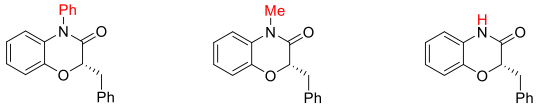
L1: R = *i*Pr (*i*Pr-BiphPHOX)
L2: R = *t*Bu (*t*Bu-BiphPHOX)

L3 (In-BiphPHOX)

L4: R = *i*Pr (*i*Pr-PHOX)
L5: R = *t*Bu (*t*Bu-PHOX)

entry	solvent	ligand[b]	conv. (%)[c]	ee (%)[d]
1	*o*-xylene	**L1**	99	97
2	*o*-xylene	**L2**	95	96
3	*o*-xylene	**L3**	96	96
4	*o*-xylene	**L4**	24	18
5	*o*-xylene	**L5**	6	42
6	DCM	**L1**	99	96
7	toluene	**L1**	99	96
8	1,4-dioxane	**L1**	99	96
9[e]	***o*-xylene**	**L1**	**99**	**97**
10[f]	*o*-xylene	**L1**	41	97
11[e,g]	*o*-xylene	**L1**	59	97

Evaluation of N-Substitution



2b, 99% conv. 89% ee

2c, 99% conv. 78% ee

2d, trace --

[a]Reaction conditions: substrate **1** (0.2 mmol), substrate/catalyst (S/C) = 100, solvent (2 mL), H_2 (60 bar). [b]Axial chirality of the catalyst was *S* when ligands L1−L3 were used. [c]Determined by ^{1}H NMR spectroscopy. [d]Determined by HPLC with a chiral column. [e]H_2 (30 bar). [f]H_2 (20 bar). [g]12 h.

products (**2p** and **2q**) were obtained in quantitative yields with 83 and 82% ee, respectively. The reduced products (**2r**−**2t**) with two substituents on the phenyl ring were also obtained with excellent enantioselectivities. The reduced product **2s** was obtained in 92% yield with 97% ee under modified reaction conditions, the two oxygen atoms of the dimethoxy group may coordinate to the catalyst, thus reducing its activity.[6l] When R^2 was another aromatic ring, the reaction proceeded well and delivered the corresponding reduced products (**2u**−**2w**) with good to excellent enantioselectivities. Heteroaromatic rings are also well tolerated in the reaction, such as 2-furanyl, 2-thienyl, and 3-thienyl groups, delivering the corresponding reduced products (**2x**−**2z**) in excellent yields. When R^2 was an alkyl substituent, the reaction also proceeded very well and afforded the corresponding reduced products (**2aa**−**2ac**) with good to excellent enantioselectivities. The cyclopropanyl group was also tolerated in the reaction, giving the product **2ac** in 98% yield with 97% ee. Next, substrates with different R^1 groups on the 1,4-benzoxazinone ring were examined. Substrates bearing an electron-donating or electron-withdrawing group at various positions of the 1,4-benzoxazinone ring delivered the reduced products (**2ad**−**2an**) in excellent results. For a substrate bearing a bromo atom on the 1,4-benzoxazinone ring with an R^2 cyclopropanyl group, the product **2ao** was obtained in 98% yield with 97% ee. The absolute configuration of the product **2v** was determined to be (*S*) by X-ray single-crystal diffraction, and the same sense of stereochemistry was assumed for the remainder of the products. In addition, we designed and carried

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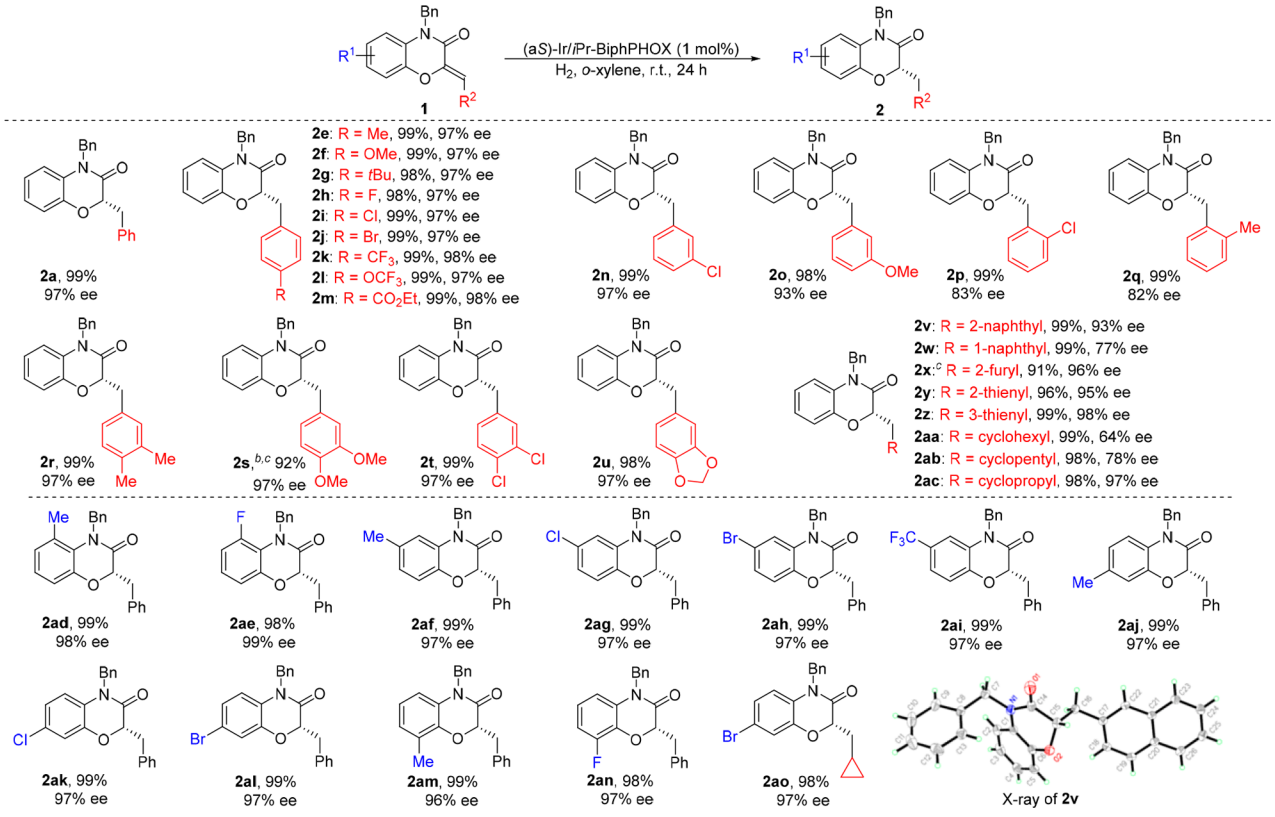
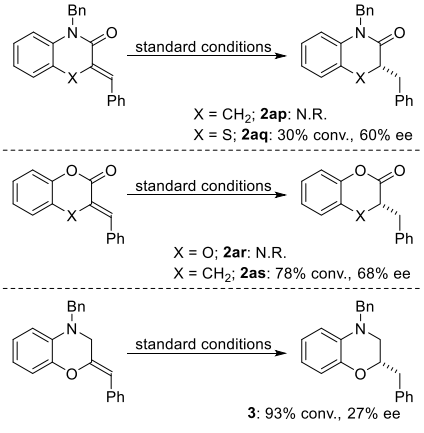
Scheme 2. Scope of the Substrate[a]



[a]Reaction conditions: substrate **1** (0.2 mmol), (a*S*)-Ir/*i*Pr-BiphPHOX (1 mol %), *o*-xylene (2 mL) under H_2 (30 bar) at r.t. for 24 h. Isolated yield. ee values were determined by HPLC with a chiral column. [b]DCE as the solvent. [c]H_2 (60 bar) and 48 h.

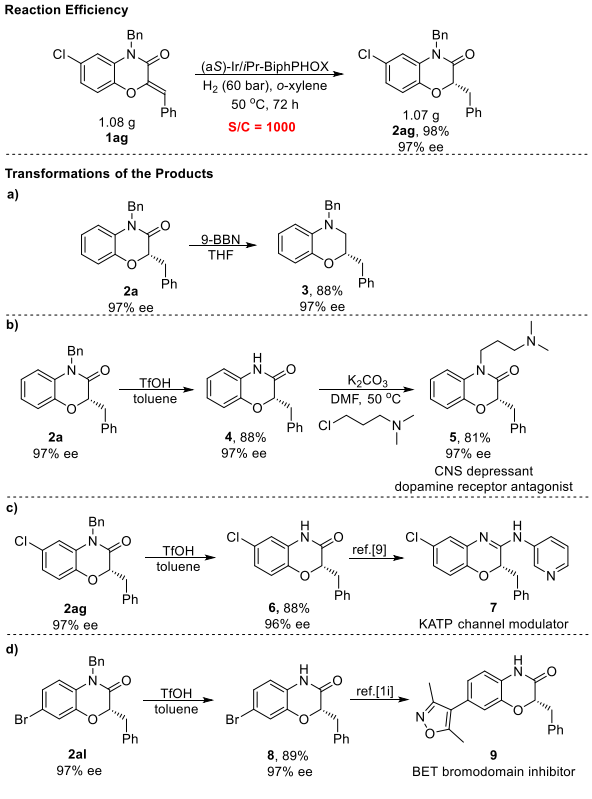
out some control experiments, and the results showed that structurally related compounds (**2ap**−**2as** and **3**) do not achieve the same levels of efficiency under the optimized reaction conditions (Scheme 3).

Scheme 3. Control Experiments



To demonstrate the efficiency and applications of this iridium-catalyzed enantioselective hydrogenation reaction, a gram-scale reaction was carried out with low catalyst loadings (0.1 mol %), giving the reduced product **2ag** in 98% yield with 97% ee (Scheme 4). Further transformations of the reduced products were also conducted. Product **2a** can be reduced with 9-BBN, providing 1,4-benzoxazine **3** in 88% yield with 97% ee (Scheme 4a). The reduced products **2a**, **2ag**, and **2al** in the

Scheme 4. Reaction Efficiency and Transformations of the Products



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presence of trifluoromethanesulfonic acid delivered the corresponding *N*-free products **4**, **6**, and **8** in good yields. Compound **4** was transformed to product **5** via a simple substitution reaction, which is a CNS depressant and a dopamine receptor antagonist (Scheme 4b).[8] Product **6** can be transformed to the ATP-sensitive potassium (KATP) channel modulator **7** according to a reported method (Scheme 4c).[9] Compound **8** is a key intermediate for the preparation of bromodomain and extraterminal (BET) bromodomain inhibitor **9** (Scheme 4d).[1i]

In summary, an efficient iridium-catalyzed enantioselective hydrogenation of 2-alkylidene 1,4-benzoxazin-3-ones using our developed axis-unfixed biphenylphosphine-oxazoline ligand has been developed, delivering chiral 2-substituted 1,4-benzoxazin-3-ones in excellent yields (up to 99%) and with excellent enantioselectivities (up to 99% ee). The reaction showed excellent functional group compatibility, and proceeded very well with low catalyst loadings (0.1 mol %) on a gram scale. Additionally, three bioactive molecules can be obtained from the reduced products.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01701.

Experimental procedures and spectral data for all new compounds (PDF)

Accession Codes

CCDC 2069776 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.

■ AUTHOR INFORMATION

Corresponding Authors

Qianjia Yuan − *Shanghai Key Laboratory of Molecular Engineering of Chiral Drugs, Frontiers Science Center for Transformative Molecules, School of Chemistry and Chemical Engineering, Shanghai Jiao Tong University, Shanghai 200240, P. R. China*; Email: yuanqianjia@sjtu.edu.cn

Wanbin Zhang − *Shanghai Key Laboratory of Molecular Engineering of Chiral Drugs, Frontiers Science Center for Transformative Molecules, School of Chemistry and Chemical Engineering, Shanghai Jiao Tong University, Shanghai 200240, P. R. China; College of Chemistry, Zhengzhou University, Zhengzhou 450052, P. R. China;* orcid.org/0000-0002-4788-4195; Email: wanbin@sjtu.edu.cn

Authors

Yu Nie − *Shanghai Key Laboratory of Molecular Engineering of Chiral Drugs, Frontiers Science Center for Transformative Molecules, School of Chemistry and Chemical Engineering, Shanghai Jiao Tong University, Shanghai 200240, P. R. China*

Jing Li − *Shanghai Key Laboratory of Molecular Engineering of Chiral Drugs, Frontiers Science Center for Transformative Molecules, School of Chemistry and Chemical Engineering, Shanghai Jiao Tong University, Shanghai 200240, P. R. China*

Jun Yan − *Shanghai Key Laboratory of Molecular Engineering of Chiral Drugs, Frontiers Science Center for Transformative Molecules, School of Chemistry and Chemical Engineering, Shanghai Jiao Tong University, Shanghai 200240, P. R. China*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.1c01701

Notes

The authors declare no competing financial interest.

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