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Iridium-Catalyzed Asymmetric Hydrogenation of 2*H*-Chromenes: A Highly Enantioselective Approach to Isoflavan Derivatives

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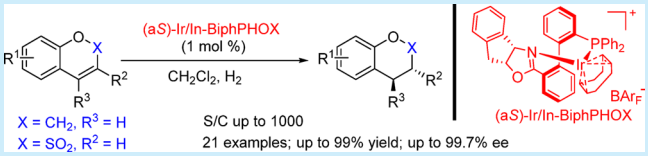
Supporting Information

ABSTRACT: A highly efficient (a*S*)-Ir/In-BiphPHOX-catalyzed asymmetric hydrogenation of substituted 2*H*-chromenes and substituted benzo[*e*][1,2]oxathiine 2,2-dioxides is described. A series of 2*H*-chromenes and benzo[*e*][1,2]oxathiine 2,2-dioxides were hydrogenated to give the target products in high yields (92−99%) with excellent enantioselectivities (up to 99.7% ee) using our catalytic system. This reaction provides a direct and efficient method for the construction of chiral benzo six-membered oxygen-containing compounds.



The dihydrobenzopyran core is a prevalent structural motif found in numerous biologically active natural compounds and pharmaceuticals. The broad range of bioactivities exhibited by molecules containing this core element has led to their description as "privileged structures" (Figure 1).[1] Among them,

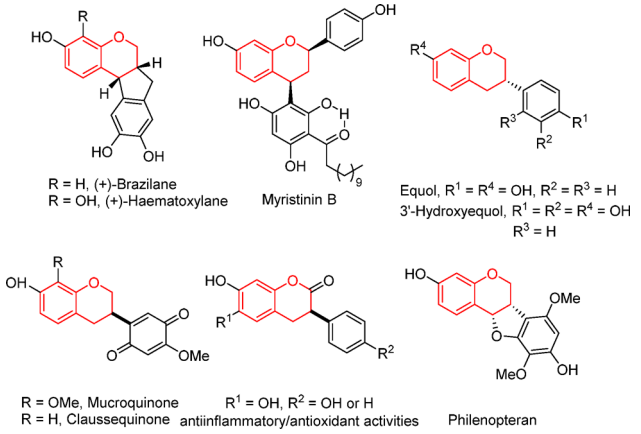


Figure 1. Representative examples of biologically active compounds possessing a chromane core.

isoflavans, which are metabolites of soy isoflavanoids, have received much attention because of their estrogenic activity, activity toward the estrogen receptor β (ERβ)[2] and potential use in menopausal hormone replacement therapy.[3] Although many synthetic methods for the racemic preparation of isoflavans have been published,[4] examples of the enantioselective synthesis of such compounds are far more rare.[5] To the best of our knowledge, the earliest conventional approaches for the preparation of this important building block employed chiral starting materials and required multistep synthetic sequences (Scheme 1a,b).[6] Although these methodologies provide a variety of routes for the preparation of isoflavans, they have several shortcomings: (1) they require an equivalent of a chiral auxiliary; (2) they suffer from limited starting material availability; and (3) they are low-yielding. Hence, exploration of new catalytic strategies for the construction of a diverse array of enantioenriched chiral dihydrobenzopyran skeletons is of great importance. Obviously, asymmetric catalysis is a good solution for these problems. In 2012, List reported a chiral Brønsted acid-catalyzed asymmetric intramolecular addition of phenol to ketene dithioacetals, and (*S*)-equol could be prepared from one of the products (Scheme 1c).[7] Metz has developed an enantioselective synthesis of isoflavanones by catalytic dynamic kinetic resolution via Ru-catalyzed asymmetric transfer hydrogenation (Scheme 1d).[8]

Asymmetric hydrogenation utilizing metal complexes has proven to be a powerful tool for the preparation of pure enantiomers because of its high efficiency, good atom economy, and minimal environmental impact.[9] Since the pioneering work of Pfaltz and co-workers,[10] iridium complexes consisting of phosphine nitrogen ligands have attracted much attention. The search for highly enantioselective and efficient reactions has prompted many chemists to design and develop new catalytic systems.[11] However, despite considerable progress in this field, efficient and straightforward syntheses of chiral dihydrobenzopyrans have rarely been reported.[12] The Zhou group reported a four-step synthetic route starting from a chiral acid obtained via Ir-catalyzed asymmetric hydrogenation of α-arylcinnamic acids using a chiral spiro phosphine−oxazoline (PHOX) ligand (Scheme 1e).[13] 4*H*-Chromene derivatives and a thio analogue have been hydrogenated with high enantioselectivities using Ir PHOX-type catalysts.[12] The asymmetric hydrogenation of 2*H*-chromenes provides a direct and efficient method for the preparation of isoflavans. We previously developed a class of axially flexible chiral phosphine−oxazoline ligands that have

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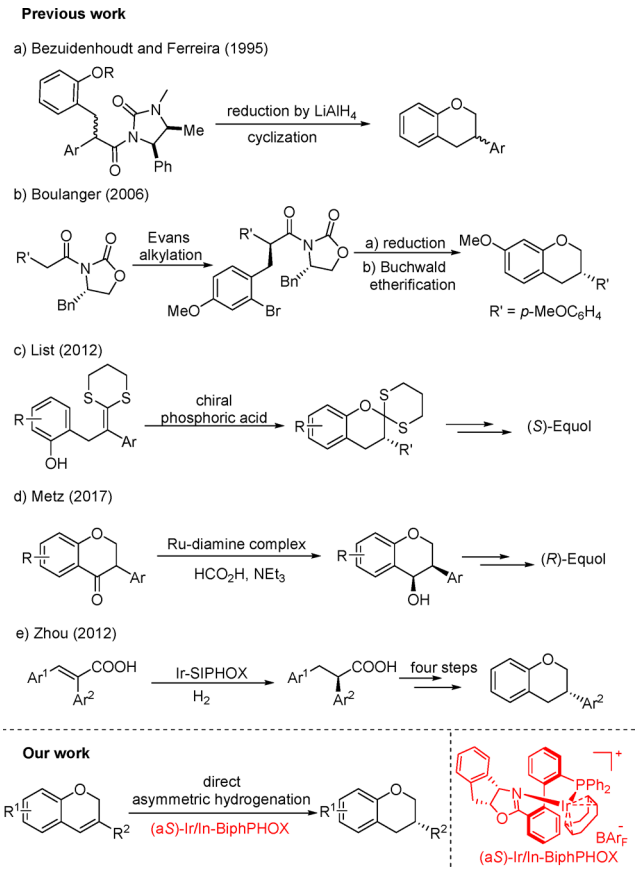
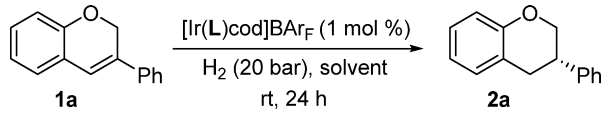
Scheme 1. Previous Reports and Our Strategy for the Enantioselective Synthesis of Isoflavans



been successfully applied in iridium-catalyzed asymmetric hydrogenations.[14] On the basis of our previous studies in this field, we expected that our catalyst would enable the asymmetric hydrogenation of 2*H*-chromenes and provide a more efficient route for the synthesis of optically pure dihydrobenzopyrans.

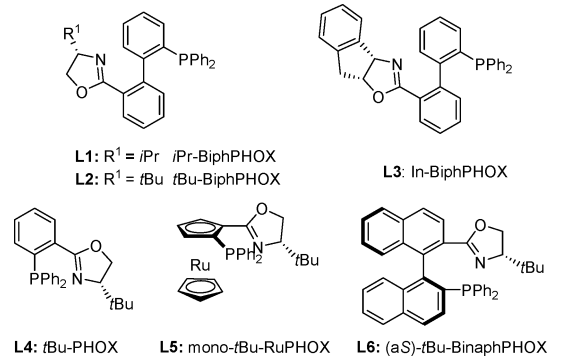
We were pleased to discover that the asymmetric hydrogenation could be conducted with our (a*S*)-Ir/In-BiphPHOX catalyst. A number of hydrogenation conditions were investigated, as shown in Table 1. We commenced our study by using **1a** as the model substrate with 1.0 mol % Ir/P,N-ligand in *o*-xylene under 20 bar hydrogen for 24 h. Initial examination of the P,N-ligated iridium catalyst showed that (a*S*)-Ir/In-BiphPHOX was the best with regard to both conversion and enantioselectivity (>99% conv, 98% ee; entry 3). Other types of axially flexible ligands, *i*Pr-BiphPHOX and *t*Bu-BiphPHOX, also gave moderate to good enantioselectivity (85% ee and 93% ee, respectively) (entries 1 and 2). Catalysis with the ligand *t*Bu-PHOX gave the desired product with poor conversion and as the opposite enantiomer (entry 4). Additionally, there was no reaction when mono-*t*Bu-RuPHOX was used as the ligand (entry 5). The ligand (a*S*)-*t*Bu-BinaphPHOX, bearing the same axial chirality as (a*S*)-Ir/In-BiphPHOX, gave the desired product with excellent enantioselectivity but poor conversion (entry 6). The effect of the solvent on the reaction was also examined with catalyst (a*S*)-Ir/In-BiphPHOX. Solvents commonly used for the Ir-catalyzed asymmetric hydrogenation of olefins (e.g., CH_2Cl_2 and toluene) allowed the reaction to proceed smoothly, providing the desired product with the same enantioselectivity

Table 1. Reaction Condition Screening[a]



entry	solvent	ligand[b]	conv (%)[c]	ee (%)[d]
1	*o*-xylene	**L1**	62	85
2	*o*-xylene	**L2**	94	93
3	*o*-xylene	**L3**	99	98
4	*o*-xylene	**L4**	46	−68
5	*o*-xylene	**L5**	NR	–
6	*o*-xylene	**L6**	16	93
7	toluene	**L3**	>99	98
8	CH_2Cl_2	**L3**	>99	98
9	$CHCl_3$	**L3**	messy	–
10	MeOH	**L3**	NR	–
11	THF	**L3**	NR	–
12[e]	CH_2Cl_2	**L3**	>99	98

[a]Reaction conditions: 0.24 mmol scale of substrate **1a**, substrate/catalyst ratio (S/C) = 100, 2 mL of solvent. [b]When **L1**−**L3** were used, the axial chirality of the catalyst was a*S*. [c]Determined by ^{1}H NMR spectroscopy. [d]Determined by HPLC using a chiral Daicel column. [e]H_2 (10 bar).



(98% ee; entries 7 and 8). However, reaction with $CHCl_3$ as a solvent was messy (entry 9). Polar solvents such as MeOH and THF were also investigated, but no hydrogenation occurred when these solvents were used (entries 10 and 11). A similar conversion and enantioselectivity were obtained when the reaction was conducted at a hydrogen pressure of 10 bar in CH_2Cl_2 (entry 12).

Under the optimal reaction conditions, a variety of 3-substituted 2*H*-chromenes were hydrogenated to the corresponding chiral 3-substituted chromanes (Scheme 2). It was found that 2*H*-chromenes bearing both electron-deficient and electron-rich mono- and disubstituted fused benzene rings could all be hydrogenated in high yields and enantioselectivities (**2a**−**g**). Substrates with different halogen groups on the benzene ring (6-, 7-, or 8-substituted groups) could all be reduced smoothly, providing the desired adducts in high yields and ee's (**2b**−**f**). Additionally, when electron-deficient or electron-rich aryl substituents were introduced as the R^2 group, the desired transformations proceeded in high yields and enantioselectivities (**2j**−**l**). Substrates bearing substituents on both of the benzene rings provided the corresponding products in excellent yields and ee's (**2h**, **2i**). Substrates bearing a disubstituted phenyl group or *β*-naphthyl group as R^2 gave the desired products with 98% ee (**2m**, **2n**). The best enantioselectivity was obtained when furyl was used as the R^2 group (99.7% ee, **2o**). The substrate bearing a methyl group as

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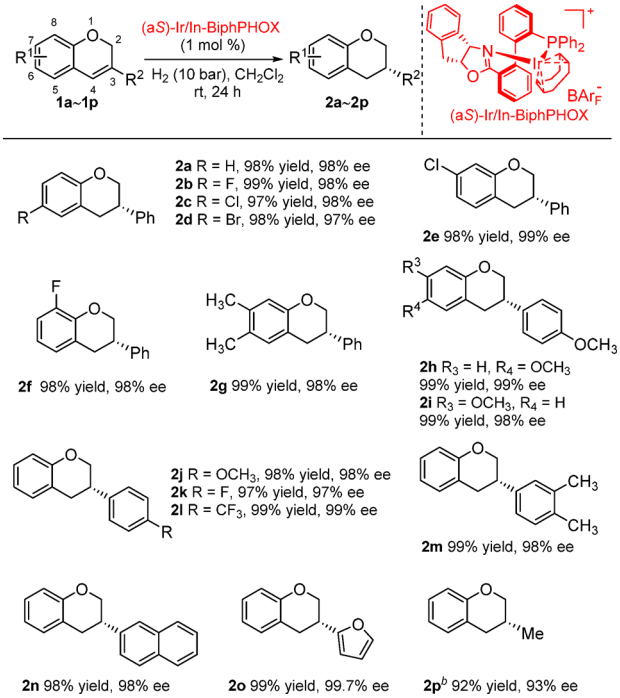
Scheme 2. Substrate Scope of 2*H*-Chromenes[a]



[a]Reaction conditions: 0.24 mmol scale of substrate, S/C = 100, 10 bar H_2, 2 mL of CH_2Cl_2, 24 h, rt. Isolated yields are shown. Enantioselectivities were determined by HPLC using a chiral column. [b]H_2 (50 bar).

R^2 also gave the corresponding product **2p** in excellent yield with good ee, albeit under a high hydrogen pressure. The absolute configuration of product **2e** was unambiguously determined to be *S* by X-ray crystallographic analysis (Figure 2).[15]

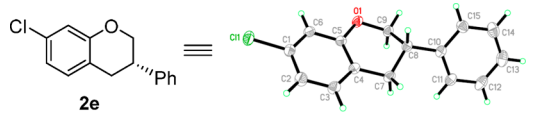
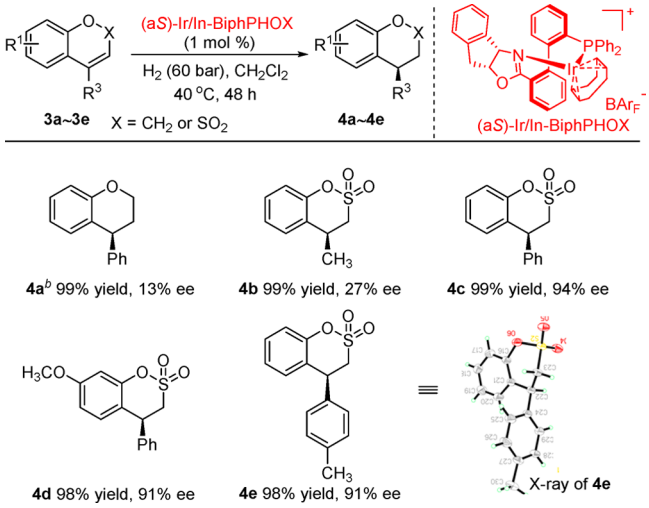


Figure 2. X-ray structure of **2e**.

Other types of benzo-fused oxygen-containing six-membered-ring substrates were also tested with our catalyst system. 4-Phenyl-2*H*-chromene (**3a**) was hydrogenated with poor enantioselectivity (**4a**).[16] Pleasingly, benzo[*e*][1,2]oxathiine 2,2-dioxides **3b**−**e** could be hydrogenated with good results. The corresponding products are important skeletons present in bioactive compounds,[17] and asymmetric syntheses of such molecules have not been widely reported (Scheme 3).[18] For example, Hayashi reported an asymmetric addition of arylboronic acids to *α,β*-unsaturated sulfonyl compounds in the presence of a rhodium catalyst coordinated with a chiral diene ligand.[18c] With our catalytic system, these types of compounds could also be prepared with full conversion when the reaction was conducted under a hydrogen pressure of 60 bar at 40 °C. Although the desired product was obtained with only 27% ee when R^3 was methyl (**4b**), the enantioselectivity increased greatly to 94% ee when R^3 was changed to a phenyl group. Substrates with a methoxy group at the 7-position or a methyl group at the *para* position of the phenyl ring could also be reduced to the desired products, albeit with a slight decrease

Scheme 3. Substrate Scope of Benzo[*e*][1,2]oxathiine 2,2-Dioxides[a]

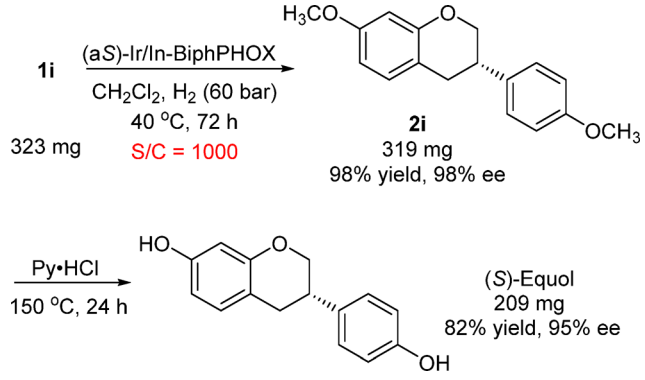


[a]Reaction conditions: 0.24 mmol scale of substrate, S/C = 100, 60 bar H_2, 2 mL of CH_2Cl_2, 48 h, 40 °C. Isolated yields are shown. Enantioselectivities were determined by HPLC using a chiral column. [b]For the reaction conditions, see Scheme 2.

in enantioselective excess (**4d**, **4e**). The absolute configuration of product **4e** was determined to be *S* by X-ray crystallographic analysis.[15]

We next investigated the synthesis of the bioactive compound (*S*)-equol using our Ir/In-BiphPHOX catalytic system. Excellent catalytic results (98% ee) were obtained when the substrate to catalyst ratio (S/C) was 1000. (*S*)-Equol could be obtained in 82% yield with 95% ee via the removal of the Me groups according to a literature procedure.[6b] Our catalyst system provides an efficient and enantioselective synthesis of (*S*)-equol via asymmetric hydrogenation (Scheme 4).

Scheme 4. Larger-Scale Synthesis of (*S*)-Equol by Asymmetric Hydrogenation



In conclusion, we have developed a highly efficient iridium-catalyzed asymmetric hydrogenation of substituted 2*H*-chromenes and 4-substituted benzo[*e*][1,2]oxathiine 2,2-dioxides in excellent yields and enantioselectivities. A direct and efficient route for the construction of chiral (*S*)-equol was successfully achieved.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02341.

Details of experimental procedures, characterization data, and copies of ^{1}H and ^{13}C NMR spectra and HPLC charts for new compounds (PDF)
X-ray data for **2e** (CIF)
X-ray data for **4e** (CIF)

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Notes

The authors declare no competing financial interest.

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