Asymmetric Catalysis

Iridium-Catalyzed Enantioselective Hydrogenation of Indole and Benzofuran Derivatives

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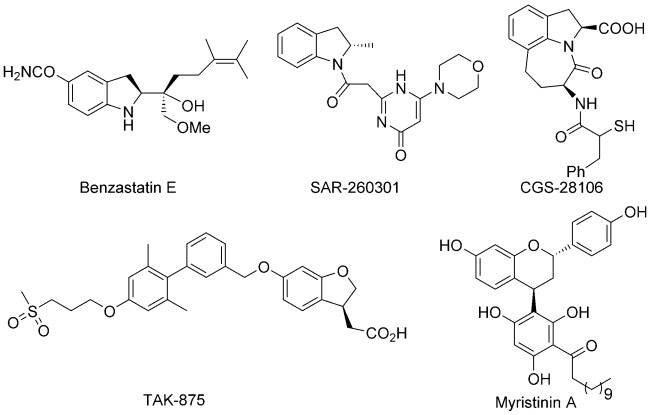
Dedication to the 1000th issue of Chemistry—A European Journal

Abstract: Enantioselective hydrogenation of a broad spectrum of N-, O-, and S-containing aromatic benzoheterocycles or nonaromatic unsaturated heterocycles has been realized by using an Ir/SpinPHOX (SpinPHOX = spiro[4,4]-1,6-nonadiene-based phosphine-oxazoline) complex as the catalyst, affording an array of the corresponding chiral benzoheterocycles (30 examples) with excellent enantioselectivities (> 99% *ee* in most cases) and turnover numbers up to 500.

Chiral heterocyclic structures are ubiquitous in natural products and artificial bioactive molecules.[1] Especially, chiral benzoheterocycles, such as indoline, 2,3-dihydrobenzofuran, and isoflavan structural moieties have been found in numerous bioactive natural products[1a,e] and drugs[1b–d] (e.g., Scheme 1). Accordingly, the development of synthetic methodologies for quick access to these chiral heterocycles is highly desirable for natural product synthesis and drug discovery. Transition-metal-catalyzed asymmetric hydrogenation (AH) of heteroaromatics is one of the most straightforward methods for the synthesis of chiral heterocycles, and a number of chiral catalysts based on transition metals have been developed for this purpose over the last two decades.[2] However, owing to the distinct stereoelectronic natures of heteroaromatic compounds, the identification of a single widely usable catalyst can be challenging. In the present communication, we report our results on the use of SpinPHOX/Ir^{I} (SpinPHOX = spiro[4,4]-1,6-nonadiene-based phosphine-oxazoline) as a versatile catalyst for AH of a diverse range of heteroaromatics (indoles and benzofurans) and nonaromatic unsaturated heterocycles (2*H*-chromenes and benzo[*b*]thiophene 1,1-dioxides), achieving high activity (turnover number (TON) up to 500) and excellent enantioselectivities (normally > 99% *ee*).



Scheme 1. Representative benzoheterocyclic compounds with pharmacological interests.

AH of the readily available indoles provides an efficient route to optically active indolines.[3] It is worthy to note that since the seminal work by Ito and co-workers in 2000,[4a] AH of various indole derivatives, either N-protected or unprotected, has been achieved by using chiral catalysts based on Rh,[4] Ru,[5] Pd,[6] or Ir[7] with limited successes. On the other hand, organocatalyzed asymmetric reduction of N-unprotected indoles has also been developed.[8] Despite these significant advances, however, most of these catalytic systems still suffer from limitations in the substituent diversity of indoles and/or functional-group tolerance. Given these considerations, we commenced the study on the AH of this type of heteroaromatics by using chiral SpinPHOX/Ir^{I} catalysts[9] developed in our lab.

The reaction was initially carried out by using the *N*-Boc-2-methylindole **2a** (Boc = *tert*-butyloxycarbonyl) as a test substrate and 1 mol% of SpinPHOX/Ir^{I} complexes **1a**–**e** as the catalyst. The reaction was typically performed under 50 atm of H_2 in dichloromethane at room temperature for 24 h, and the results were summarized in Table 1. Under the otherwise identical conditions, both (*S*,*S*)-**1a** and (*R*,*S*)-**1a** catalyzed the hydrogenation of **2a**, with the (*R*,*S*)-**1a** leading to a relatively higher substrate conversion (Table 1, entry 1 vs. 2). On the other hand,

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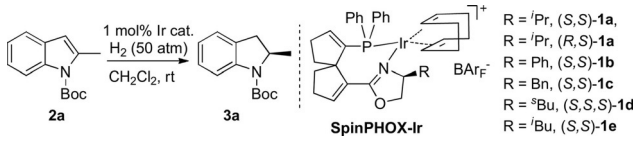
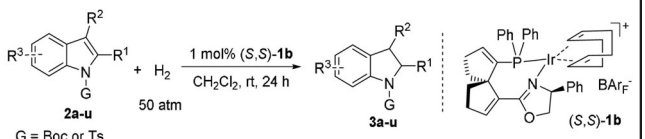
Table 1. SpinPHOX/Ir^{I}-catalyzed AH of **2a**.[a]

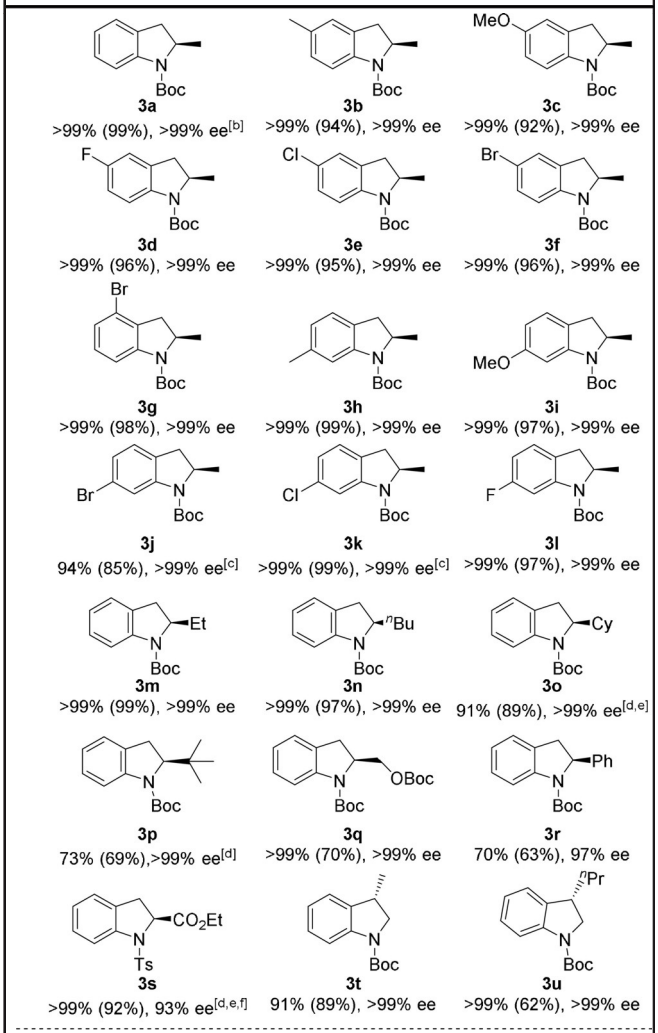


Entry	Ir catalyst	Conversion [%][b]	*ee* [%][c]
1	(*R*,*S*)-**1a**	>99	78
2	(*S*,*S*)-**1a**	73	95
3	(*S*,*S*)-**1b**	>99	>99
4	(*S*,*S*)-**1c**	39	73
5	(*S*,*S*,*S*)-**1d**	73	94
6	(*S*,*S*)-**1e**	>99	75

[a] All reactions were conducted with 0.2 mmol of **2a** in the presence of 0.002 mmol of Ir^{I} catalyst (1 mol%) under 50 atm of H_2 in 2.5 mL of CH_2Cl_2 at room temperature for 24 h. [b] Determined by ^{1}H NMR spectroscopy. [c] The *ee* values were determined by HPLC analysis on a chiral stationary phase.

Table 2. AH of **2a–u** catalyzed by iridium(I) catalyst (*S*,*S*)-**1b**.[a]





[a] Conditions: **2** (0.2 mmol), (*S*,*S*)-**1b** (0.002 mmol), CH_2Cl_2 (2.5 mL), $p(H_2)$ (50 atm), 25 °C, 24 h. The substrate conversions (values before the parentheses) were determined by ^{1}H NMR analyses, and the values within the parentheses are yields of the isolated products **3a–u**. The absolute configurations of **3a–u** were assigned by comparison of their optical rotations with the literature reported values or based on their circular dichroism (CD) spectra (see the Supporting Information). [b] **2a** (1 g, 4.3 mmol), (*S*,*S*)-**1b** (14 mg, 0.0086 mmol), $p(H_2)$ (80 atm). [c] **2j–k** (0.1 mmol), (*S*,*S*)-**1b** (0.002 mmol). [d] **2o–p** and **2s** (0.04 mmol), (*S*,*S*)-**1b** (0.002 mmol). [e] $p(H_2)$ (80 atm). [f] 50 °C.

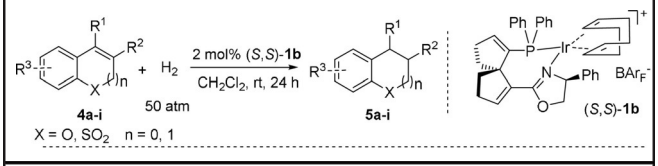
the reaction catalyzed by (*S*,*S*)-**1a** afforded the product (*R*)-**3a** with a much better enantioselectivity (95% *ee*), indicating an (*S*)-spiro backbone and *S*-oxazolyl moiety constitutes a matched pair of chiralities for the SpinPHOX/Ir^{I} catalysts in this reaction. Further survey of the Ir^{I} complexes (*S*,*S*)-**1b–e** revealed that the oxazolyl substituent on the SpinPHOX ligand have a remarkable influence on both the reactivity and enantioselectivity of the catalysis, delivering (*R*)-**3a** with good to excellent *ee* values (73–>99%) in varied substrate conversions (33->99%) (Table 1, entries 3–6). Complex (*S*,*S*)-**1b**, bearing a Ph group on the oxazoline ring, turned out to be optimal for both reactivity and enantiocontrol of the reaction, affording the indoline (*R*)-**3a**, a synthetic precursor to the enantiomer of (*S*)-SAR-260301,[1b] with full conversion and >99% *ee* (Table 1, entry 3).

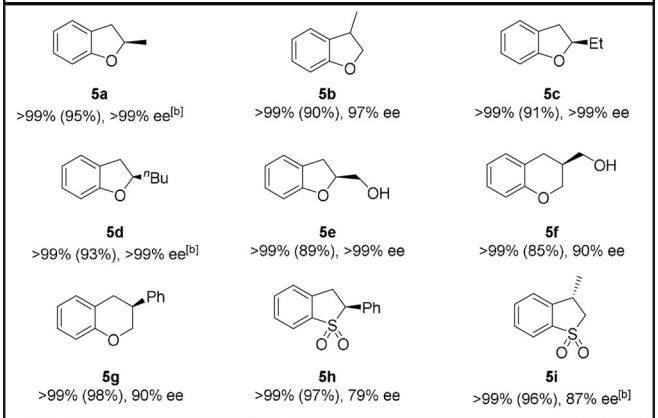
Subsequently, the AH of a variety of N-protected indoles **2a–u** were examined under the optimized conditions. As shown in Table 2, catalyst (*S*,*S*)-**1b** was found to be highly enantioselective for various *N*-Boc- or *N*-Ts-indole (Ts = *p*-toluenesulfonyl) derivatives, affording the corresponding indolines with >99% *ee* in most cases. The protocol demonstrated a high compatibility with the phenyl moieties of *N*-Boc-indoles **2a–l**, as the corresponding products **3a–l** were obtained all in >99% *ee* values, irrespective of the electron-donating/-withdrawing nature, identity, or location of the substituents (R^3) on the phenyl rings. Further application of the protocol to other 2-substituted (2-Et, -*n*Bu, -Cy (Cy = cyclohexyl), -*t*Bu, 2-CH_2OBoc, or -Ph) indoles **2m--r** also proved to be successful, and the corresponding hydrogenation products **3m--r** were obtained with consistently excellent enantioselectivities (97–>99% *ee*), albeit in some cases in slightly diminished yields as a result of incomplete conversion (**2o**, **2p**, **2r**) or partial decomposition (**2q**) of the substrates. However, in the hydrogenation of ethyl *N*-Boc-indole-2-carboxylate, partial cleavage of the Boc group of the starting material (ca 19%) was observed under the reaction conditions. This difficulty was circumvented by switching the protecting group from Boc to Ts. Hydrogenation of *N*-Ts-protected indole **2s** proceeded smoothly under slightly modified conditions (80 atm H_2, 50 °C, 5 mol% **1b**), to deliver **3s** in high yield (92%) and excellent *ee* (93%). It is noteworthy that ethyl indoline-2-carboxylate, the N-detosylated product of **3s**, has been used as the key intermediate for synthesis of natural product benzastatin E,[1a] angiotensin-converting-enzyme inhibitor pentopril,[1j] and antihypertensive agent 1-(3-mercapto-2-methyl-l-oxopropyl)indoline-2-carboxylic acid.[1k] To our de-

light, the same catalyst (*S*,*S*)-**1b** was also applicable to the hydrogenation of 3-alkyl-substituted *N*-Boc-indoles. Under standard conditions, the hydrogenation of 3-methylindole derivative **2t** gave (*S*)-3-methylindoline **3t** in high yield (89%) and >99% *ee*. For the AH of 3-allyl *N*-Boc-indole derivative **2u**, both C=C bonds of the allyl substituent and pyrrolyl ring were reduced, affording (*S*)-3-*n*-propylindoline **3u** in 62% yield with >99% *ee*. By comparison of the optical rotations with the literature reported values or CD spectra, the absolute configurations for products **3a**–**n** were determined to be *R*, whereas those for **3o**--**u** were *S*. Remarkably, this protocol can be readily scaled-up to AH of 1.0 g of **2a**. In the presence of 0.2 mol% (*S*,*S*)-**1b**, the hydrogenation proceeded smoothly under 80 atm H_2 to provide (*R*)-**3a** in nearly quantitative yield with >99% *ee*.

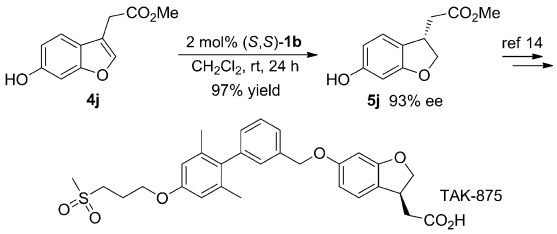
Encouraged by the good performance of (*S*,*S*)-**1b** in the AH of N-protected indoles, we proceeded to extend this catalytic system to the AH of several types of unsaturated O- or S-containing heterocyclic compounds, including benzofurans, substituted 2*H*-chromenes, and benzothiophene 1,1-dioxides. It is noteworthy that compared with indoles, the AH of benzofurans has been much less explored.[10] For Ir-catalyzed AH of benzofurans, Pfaltz and co-workers described the use of some bicyclic pyridine-phosphinite iridium complexes, providing the corresponding products in high yields with good to excellent enantioselectivities, albeit slightly elevated temperatures (40–60 °C) are required for substrate conversions.[10b,c] As shown in Table 3, catalyst **1b** proved to be effective in AH of 2- or 3-alkyl or hydroxymethyl-substituted benzofurans **4a**–**e.** The hydrogenation proceeded smoothly, affording exclusively the corresponding heterocyclic ring-reduced products **5a**–**e** in high yields with excellent enantioselectivities (97–>99% *ee*). Although the AH of 2*H*-chromenes can provide a straightforward access to chiral isoflavans that are present in numerous bioactive compounds and pharmaceuticals,[1e,11] the only catalyst system documented so far was reported by Zhang et al. in 2017.[12] To our delight, (2*H*-chromen-3-yl)methanol and 3-phenyl-2*H*-chromene were hydrogenated to the corresponding chiral 3-substituted chromanes **5f** and **5g** in good yields with high enantioselectivities by using the same catalyst (*S*,*S*)-**1b**. The hydroxyl group was compatible in the hydrogenation of **4e** and **4f**, which may benefit the synthesis of further complex chiral dihydrobenzofuran and chromane-derived compounds. AH of benzo[*b*]thiophene 1,1-dioxides can provide optically enriched 2,3-dihydrobenzo[*b*]thiophene 1,1-dioxides, which have found interest as herbicides and insecticides.[13] Recently, Pfaltz and Tosatti[14a] and Zhang et al.[14b] have independently reported enantioselective hydrogenation of benzo[*b*]thiophene 1,1-dioxides by using Ir- or Rh-based complexes as catalysts. When using (*S*,*S*)-**1b** as the catalyst, AH of 2-phenyl- or 3-methyl-substituted benzo[*b*]thiophene 1,1-dioxides **4h** and **4i** also performed well under standard conditions, delivering the hydrogenated products **5h** and **5i**, respectively, in high yields and good enantioselectivities. To further showcase the utility of this protocol, the hydrogenation of benzofuran derivative **4j** was performed in the presence of 2 mol% (*S*,*S*)-**1b**. The corresponding 2,3-dihydrobenzofuran **5j**, a key chiral intermediate for the synthesis of novel antidiabetic agent TAK-875,[15] was produced in 97% yield with 93% *ee* (Scheme 2).

Table 3. AH of benzofurans, 2*H*-chromenes, benzothiophene 1,1-dioxides by iridium(I) catalyst (*S*,*S*)-**1b**.[a]





[a] Conditions: **4** (0.1 mmol), (*S*,*S*)-**1b** (0.002 mmol), CH_2Cl_2 (2.5 mL), $p(H_2)$ (50 atm), 25 °C, 24 h. The substrate conversions were determined by ^1H NMR analyses, and the values within the parentheses are yields of the isolated products **5a**–**i**. The absolute configurations of **5a**–**i** were assigned by comparison of their optical rotations with the literature reported values or based on their CD spectra (see the Supporting Information). [b] 1 mol% catalyst.



Scheme 2. Hydrogenation of benzofuran derivative **4j** for formal synthesis of TAK-875.

Whereas extensive experimental and theoretical studies have been performed by the groups of Andersson,[16a,e,f] Pfaltz,[16b,i] Burgess,[16c] and others,[16g,j,l] there is still no consensus regarding the mechanistic details for Ir-catalyzed asymmetric hydrogenation of prochiral heteroaromatics. Given the excellent catalytic performance of (*S*,*S*)-**1b** in the AH of unsaturated heterocyclic compounds, we proceeded to study the solution structures of the precatalyst by using NMR techniques to gather some preliminary data that are valuable for mechanistic understandings. Treatment of a [D_8]THF solution of (*S*,*S*)-**1b** with hydrogen bubbles in the NMR tube at −60 °C for 10 min, resulted in a mixture of species that displayed three new signals in the hydride region of its ^1H NMR spectrum. As shown in Figure 1a, the ^1H NMR spectrum reveals only few res-

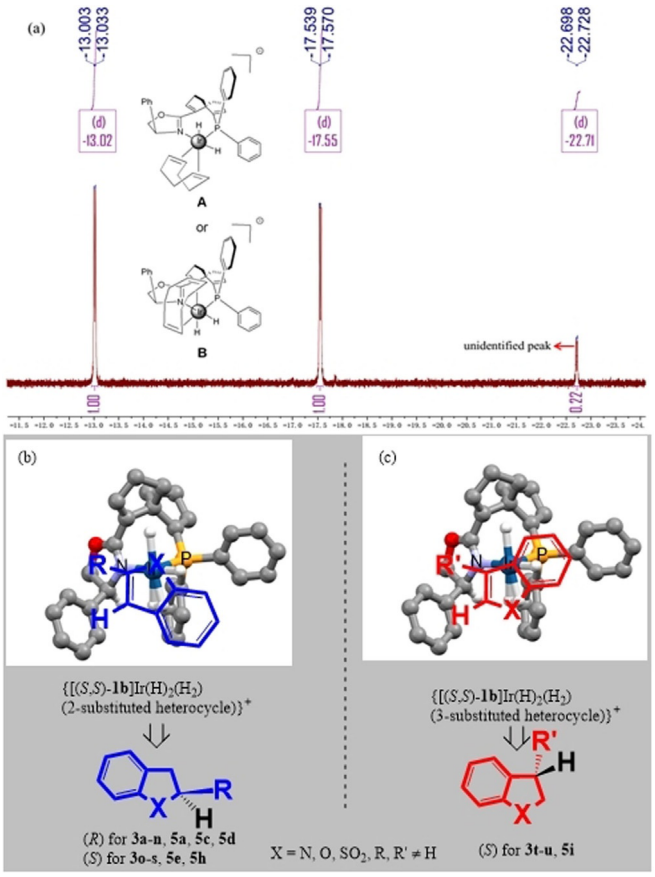


Figure 1. a) ^{1}H NMR spectrum (hydride region, 600 MHz) of (*S*,*S*)-**1 b** after treatment with hydrogen bubbles in [D$_8$]THF at −60 °C for 10 min. b,c) Schematic models for the enantioselection in AH of 2- and 3-substituted unsaturated heterocycles, respectively.

onances in the hydride region, indicating that only a limited number of iridium hydride species are produced under these conditions. Notably, a pair of intense doublets are found with equal integrals at $\delta = -13.02$ (^{2}J(H,P) = 18.0 Hz) and −17.55 ppm (^{2}J(H,P) = 18.1 Hz), respectively. ^{1}H, ^{31}P, ^{1}H–^{1}H COSY, and ^{31}P–^{1}H COSY experiments (see the Supporting Information) clearly show that these signals are corresponding to two hydrides located on a single Ir center, and the ^{2}J(H,P) values of 18 Hz clearly indicated that both hydrides are disposed *cis* to the phosphorus atom in the Ir complex. This dihydride complex can be formulated as the cationic species [(SpinPHOX)Ir(H)$_2$(cod)]$^+$ (COD = 1,5-cyclooctadiene) **A** or its isomer **B** (Figure 1 a), analogous to those reported by Pfaltz and co-workers for [(PHOX)Ir(H)$_2$(cod)]$^+$,[16b] considering the close resemblance of both chemical shifts and coupling constants with those data. A weak doublet at $\delta = -22.7$ ppm (^{2}J(H,P) = 17.8 Hz) was also visible, corresponding to some type of unknown hydride species present in minor amount. Based on these results and the X-ray crystallographic structure of (*S*,*S*)-**1 b**[9c] as well as the elegant theoretical study by Andersson and co-workers on Ir/P N-catalyzed AH of unfunctionalized olefins,[16e] we tentatively proposed a schematic model for stereoselection in the titled reaction. As shown in Figures 1 b and c, in the key intermediate {[(*S*,*S*)-**1 b**]Ir(H)$_2$(H$_2$)(substrate)}$^+$, the Ph substituent of oxazolyl moiety is situated below the N-Ir-P plane as a result of constraints by the rigid ligand backbone. As a trisubstituted olefin, the 2- or 3-substituted heterocycle is coordinated with its C=C double bound to Ir in a site *trans* to P atom, and oriented with its smallest substituent (H) pointing towards the oxazolyl phenyl group to minimize steric repulsions. According to these enantioselection models, the predicted absolute configurations for the products **3 a**–**n**, **5 a**, **5 c**, and **5 d** should be *R*, whereas those for the rest should be *S*, which are all in excellent agreement with the experimental observations (Tables 2 and 3).

In summary, we have disclosed that the SpinPHOX/Ir^{I} complex (*S*,*S*)-**1 b** is a highly efficient and versatile catalyst for enantioselective hydrogenation of a broad range of electron rich heteroaromatics, including *N*-Boc-protected-indoles and benzofurans, as well as benzoheterocycles, such as substituted 2*H*-chromenes and benzo[*b*]thiophene 1,1-dioxides, which are generally regarded as challenging substrates for transition-metal-catalyzed asymmetric hydrogenation. High activities (TON up to 500) were obtained, and excellent enantioselectivities (>99% *ee*) have been achieved in most cases. The salient features of broad substrate scope, excellent enantioselectivity, and operational simplicity, may render the protocol useful for further applications in the synthesis of various chiral heterocyclic compounds.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: asymmetric catalysis · benzofurans · benzothiophene 1,1-dioxides · hydrogenation · indoles · iridium

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