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Ir-SpinPHOX Catalyzed Enantioselective Hydrogenation of 3-Ylidenephthalides

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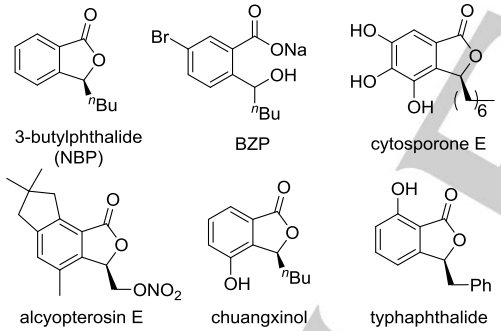
Dedication ((optional))

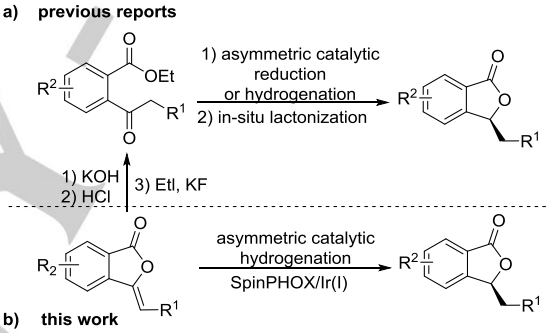
Abstract: The first asymmetric hydrogenation of 3-ylidenephthalides has been developed using the Ir^{I} complex of a spiro[4,4]-1,6-nonadiene-based phosphine–oxazoline ligand (SpinPHOX) as the catalyst, affording a wide variety of chiral 3-substituted phthalides in excellent enantiomeric excesses (up to 98% ee). The utility of the protocol has been demonstrated in the asymmetric synthesis of chiral drugs NBP and BZP precursor, as well as the natural products chuangxinol and typhaphthalide.

The phthalide[1(3*H*)-isobenzofuranone] frameworks, in particular chiral 3-substituted phthalides, are structural subunits in numerous natural products with remarkable pharmaceutical interests (Scheme 1).[1] For examples, (*S*)-3-*n*-butylphthalide (NBP), a constituent of celery seed oil, and its derivative BZP demonstrate diverse pharmacological effects for anti-tumor, anti-asthmatic, anti-convulsant, anesthesia prolongation, and have been clinically approved as anti-ischemic agents by CFDA.[2] Cytosporone E[3] and alcyopterosin E[4] exhibit antibacterial activity and cytotoxicity against wild Hep-2 cell line, respectively.



Scheme 1. Representative phthalide natural products and derivatives with pharmacological interests.

Such broad spectra of biological activities made chiral 3-substituted phthalides attractive synthetic targets, and much efforts have been devoted to access these important architectures.[5] In this context, conventional methods usually involved multistep synthesis using chiral auxiliaries,[6] or optical resolution in a few cases.[7] The asymmetric catalytic strategies developed for 3-substituted chiral phthalides were mostly based on the conversion of 2-acylarylcarboxylates into the enantioenriched 2-(hydroxymethyl) arylcarboxylates via asymmetric hydrogenation (AH),[8] transfer hydrogenation,[9] or organometallic addition,[10] followed by an in situ lactonization (Scheme 2a). Alternative asymmetric catalytic methods via dihydroxylation and lactonization,[11] ketone hydroacylation,[12] or redox allylation[13] have also been explored.



Scheme 2. Asymmetric catalytic synthesis of phthalide derivatives.

We envisioned that the AH of readily accessible 3-ylidenephthalides,[14] which are synthetic precursors for 2-acylarylcarboxylates, might constitute a more straightforward approach to enantioenriched 3-substituted phthalides (Scheme 2b). Although there have been a few literature precedents on the AH of several simple lactones bearing an exocyclic methylene moiety (e.g., 5-methylideneoxolan-2-one, 5-methylene-1,3-dioxolan-2-one, and 6-methylene-tetrahydropyran-2-one),[15] AH of 3-ylidenephthalide derivatives has not been reported so far, probably due to the difficulty associated with chelation of exocyclic C=C bond to the catalyst metal, which is often crucial for effective chirality transfer especially in Rh or Ru catalyzed AH of olefins.[16] On the other hand, AH of minimally functionalized olefins with various chiral Ir-P^N catalysts has received considerable attention[17] since the pioneering work reported by Pfaltz and coworkers.[18] We previously reported a class of chiral iridium(I) complexes with spiro P^N ligands, SpinPHOX/Ir(I), for efficient AH of ketimines and several types of α,β-unsaturated carbonyl compounds.[19] In continuation of our work along this vein, herein we communicate the AH of 3-alkylidene- and 3-arylidenephthalides with a SpinPHOX/Ir(I) catalyst, providing a direct access to chiral 3-substituted phthalides in excellent enantiopurities.

Our initial evaluation began with AH of **5a** as the model substrate. The reaction was performed in CH_2Cl_2 at rt under 50 atm H_2 in the presence of 1 mol% (*R*,*S*)-**1a** as the catalyst. Full

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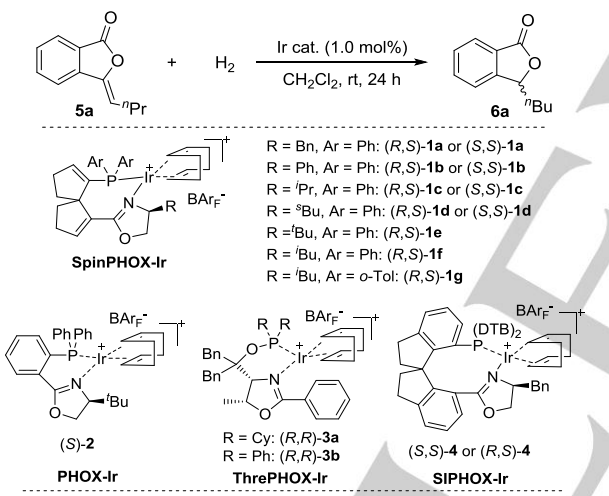
conversion to **6a** with 88% ee was observed in 24 h (Table 1, entry 1), which encouraged us to further screen the SpinPHOX/Ir(I) series [(*R*,*S*)-**1a-g**, (*S*,*S*)-**1a-d**] under identical conditions. The axial chirality of the SpinPHOX ligands seems to play a dominant role in the sense of the asymmetric induction (entries 1-10), and the (*R*,*S*)-**1** (entries 1, 3, 5, 7) gave much higher enantioselectivities than their corresponding mismatched diastereomeric (*S*,*S*)-counterparts (entries 2, 4, 6, 8). Moreover, the oxazoline substituent also has an impact on the asymmetric induction and/or catalytic activity. Catalysts (*R*,*S*)-**1a**, (*R*,*S*)-**1d** and (*R*,*S*)-**1f** bearing a Bn, ^{s}Bu or ^{i}Bu group on their oxazoline moieties, respectively, were superior in terms of both reactivity and enantioselectivity, affording a full conversion to **6a** with 87-88% ee (entries 1, 7, 10). With 0.5 mol% of (*R*,*S*)-**1f** as the catalyst, AH of **5a** under 30 atm of H_2 proceeded to completion in 4 h with 91% ee for **6a** (entry 11). Using (*R*,*S*)-**1g** as the catalyst in AH of **5a** gave **6a** in 93% ee (entry 12), which was improved to 95% under a lower pressure of H_2 (10 atm, entry 13). Remarkably, AH of **5a** under 2 atm H_2 with 0.5 mol% (*R*,*S*)-**1g** still proceeded to full conversion and afforded 95% ee of (*R*)-**6a** (entry 14). Several well-established chiral iridium phosphine-oxazoline catalysts, including PHOX-Ir [(*S*)-**2**],[18] ThrePHOX-Ir [(*R*,*R*)-**3a-b**],[20] and SIPHOX [(*S*,*S*)- or (*R*,*S*)-**4**],[21] were also examined in this reaction under otherwise identical conditions as in entry 11. Unfortunately, lower reactivity and/or enantioselectivity was observed in these cases (entries 15-19).

Table 1. Ir(I)-catalyzed AH of the 3-butylidenephthalide (**5a**)[a]

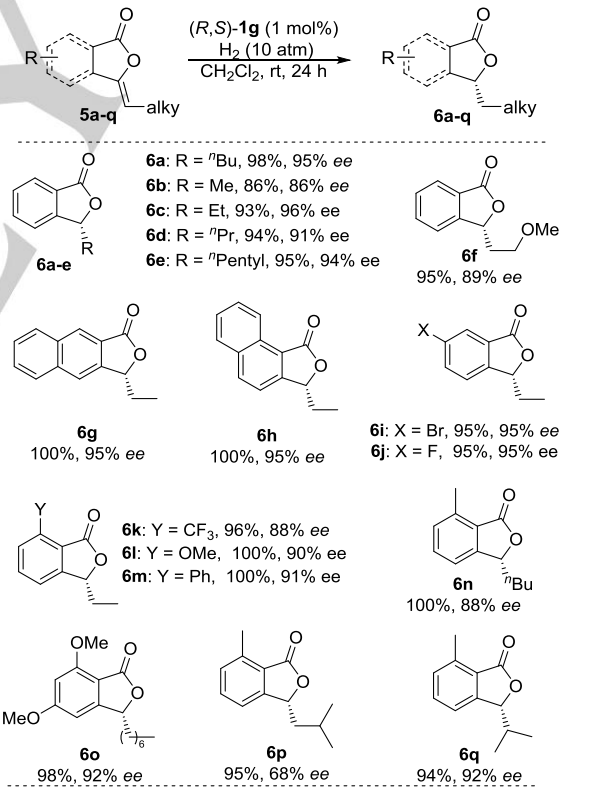


Entry	Ir Cat.	$p(H_2)$(atm)	Conv.[%][b]	Ee[%][c]
1	(*R*,*S*)-**1a**	50	> 99	88 (*R*)
2	(*S*,*S*)-**1a**	50	92	11 (*S*)
3	(*R*,*S*)-**1b**	50	> 99	67 (*R*)
4	(*S*,*S*)-**1b**	50	33	33 (*S*)
5	(*R*,*S*)-**1c**	50	80	87 (*R*)
6	(*S*,*S*)-**1c**	50	93	7 (*R*)
7	(*R*,*S*)-**1d**	50	> 99	87 (*R*)
8	(*S*,*S*)-**1d**	50	91	3 (*R*)
9	(*R*,*S*)-**1e**	50	47	73 (*R*)
10	(*R*,*S*)-**1f**	50	> 99	88 (*R*)
11[d]	(*R*,*S*)-**1f**	30	> 99	91 (*R*)
12[d]	(*R*,*S*)-**1g**	30	> 99	93 (*R*)
13[d]	(*R*,*S*)-**1g**	10	> 99	95 (*R*)
14[e]	(*R*,*S*)-**1g**	2	> 99	95 (*R*)
15	(*S*)-**2**	30	58	33 (*R*)
16	(*R*,*R*)-**3a**	30	76	81 (*S*)
17	(*R*,*R*)-**3b**	30	89	*rac*
18	(*S*,*S*)-**4**	30	14	23 (*R*)
19	(*R*,*S*)-**4**	30	0	-

[a] Conditions: **5a** (0.25 mmol), Ir cat. (0.0025 mmol), dichloromethane (2.5 mL), 25℃, 24 h. [b] Determined by ^{1}H NMR spectroscopy. [c] Determined by HPLC analysis on a chiral stationary phase. [d] 0.5 mol% of (*R*,*S*)-**1f** or (*R*,*S*)-**1g**, 4 h. [e] 0.5 mol% (*R*,*S*)-**1g**, 24 h.

With the optimal catalyst (*R*,*S*)-**1g** at hand, we proceeded to examine the substrate scope of the protocol. The 3-ylidenephthalide substrates bearing aliphatic (**5a-q**) or aromatic side moieties (**7a-q**) were readily obtained via one-step synthesis from cheap starting materials (SI). AH of these 3-ylidenephthalides proceeded smoothly with (*R*,*S*)-**1g** as the catalyst, and the results were summarized in Tables 2 and 3. The protocol proved to be versatile for AH of **5a-q** (Table 2), where the corresponding phthalides **6a-q** were generally obtained in high yields (86->99%) and good to excellent enantioselectivities (86-96% ee), irrespective of the side chain lengths (alkyl = H, Me, Et, ^{n}Pr, ^{n}Bu) or stereoelectronic nature of the substituent (MeO, naphthyl, *m*-Br, *m*-F, *o*-CF_3, *o*-OMe, *o*-Ph, *o*-Me) on the phthalide phenyl ring. An intriguing behavior was found in the AH of **5p** bearing an isopropyl group, where the phthalide **6p** was obtained in moderate ee (68%). Remarkably, AH of **5q** with a *tetra*-substituted C=C bond also proceeded smoothly to afford **6q** in > 99% yield with 92% ee.

Table 2. AH of the 3-alkylidenephthalides (**5a-q**)[a]



[a] Conditions: **5** (0.2 mmol), (*R*,*S*)-**1g** (0.002 mmol), CH_2Cl_2 (2.0 mL), $p(H_2)$ (10 atm), 25°C, 24 h. The yields are for the isolated products **6a-q**, and the ee values were determined by HPLC analysis on a chiral stationary phase. The absolute configurations of **6a-q** were assigned to be (*R*) by comparison of their optical rotations with the literature reported values or based on their CD spectra (see SI).

3-Arylidenephthalides **7a-q** turned out to be less reactive for this AH system, probably owing to the electronic stabilization of C=C bond by two conjugated aryl rings. A survey of the reaction conditions for AH of 3-benzalphthalide **7a** revealed that

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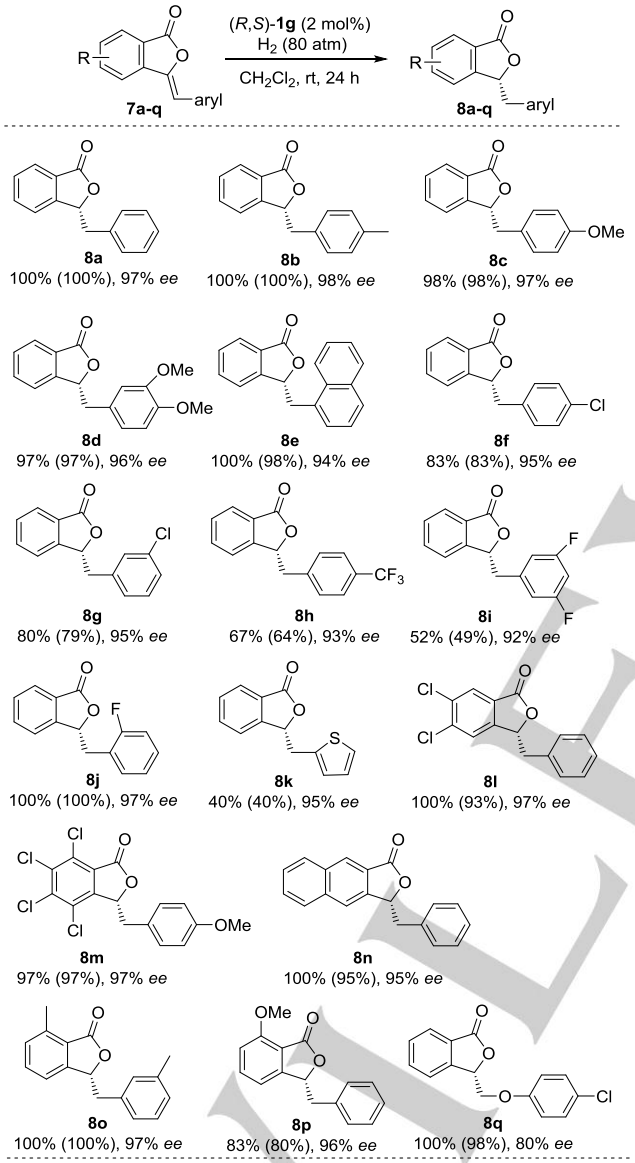
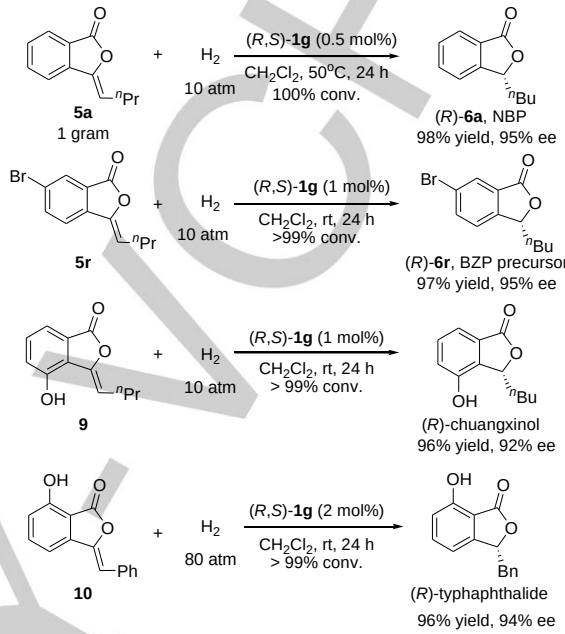
elevated H_2 pressure (80 atm) and higher loading of (*R*,*S*)-**1g** (2 mol%) were necessary for smooth conversion (see SI). Under these optimized conditions, AH of a variety of 3-arylidenephthalides (**7a-p**) were examined and the results were shown in Table 3. In all cases, the corresponding products **8a-p** were obtained with excellent enantioselectivities (92-98% ee), albeit incomplete conversions were observed for reactions of several substrates. Finally, the AH of 3-ylidenephthalide **7q** with a vinyl phenoxy ether moiety also proceeded well to afford **8q** in excellent yield (98%) with good ee value (80%).

Table 3. AH of the 3-arylidenephthalides (**7a-q**)[a]



[a] Conditions: **7** (0.1 mmol), (*R*,*S*)-**1g** (0.002 mmol), CH_2Cl_2 (4.0 mL), $p(H_2)$ (80 atm), 25°C, 24 h. The substrate conversions (values before the parentheses) were determined by ^1H NMR analyses, and the values within the parentheses are yields of the isolated products **8a-q**. The ee values were determined by HPLC analysis on a chiral stationary phase. The absolute configurations of the products were assigned to be (*R*) by comparison of their optical rotations with the literature reported values or based on their CD spectra (see SI).

The synthetic utilities of the protocol were demonstrated in the synthesis of several chiral drugs and natural products with AH of the corresponding 3-ylidenephthalides as the key steps (Scheme 3). Under standard reaction conditions, (*R*,*S*)-**1g** catalyzed AH of **5a** was performed on gram-scale to afford (*R*)-NBP (**6a**) in nearly quantitative yield with 95% ee. Under identical reaction conditions, AH of 3-ylidenephthalide **5r** gave 95% ee of (*R*)-**6r**, which is an immediate synthetic precursor to BZP,[2b-c] a potential cardiovascular drug. Finally, AH of phenoxy-bearing 3-ylidenephthalides **9** and **10** with (*R*, *S*)-**1g** as the catalyst provided ready access to optically active natural products (*R*)-chuangxinol[22] and (*R*)-typhaphthalide,[23] respectively, in high yields and excellent ee values.



Scheme 3. Synthesis of chiral drugs NBP and BZP precursor, as well as the natural products (*R*)-chuangxinol and (*R*)-typhaphthalide with AH of 3-ylidenephthalides as the key steps

We have determined the solid structure of catalyst precursor (*R*,*S*)-**1g** (Figure 1a). Inspired by the elegant theoretical study of Andersson and coworkers on Ir/P^N catalyzed AH of unfunctionalized olefins,[24] we tentatively proposed a schematic model for stereoselection in the titled reaction. As shown in Figure 1b, the oxazolyl substituent R' is situated above the N–Ir–P plane of intermediate $\{[(R,S)\text{-}\mathbf{1}]Ir(H)_2(H_2)(\mathbf{5})\}^+$, as a result of constraints by the rigid ligand backbone. As a trisubstituted olefin, 3-ylidenephthalide is coordinated *trans* to P and oriented with its smallest substituent (H) pointing towards the oxazoline fragment, hence leading to preferential formation of (*R*)-phthalides.

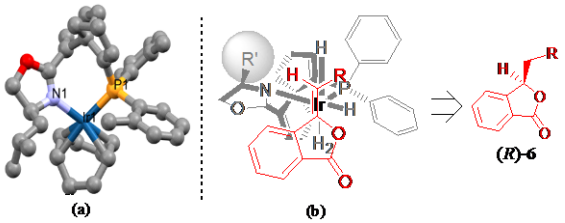


Figure 1. (a) X-Ray structures of (*R*,*S*)-**1g**, H atoms and BAr_F^- anion are omitted for clarity. (b) Schematic model for enantioselection of (*R*,*S*)-**1**.

In summary, we have developed the first enantioselective hydrogenation of 3-ylidenephthalides using a SpinPHOX/Ir(I) catalyst, providing a straightforward approach to a wide variety of 3-substituted chiral phthalides in high yields with excellent optical purities (up to 98 % ee). Synthetic utilities of the protocol have also been demonstrated in the asymmetric synthesis of chiral drugs (*R*)-NBP and a (*R*)-BZP precursor, as well as the natural products (*R*)-chuangxinol and (*R*)-typhaphthalide. Given the considerable biological importance, the protocol might find broader applications

in asymmetric synthesis of chiral 3-substituted phthalides of medicinal interest.

Acknowledgements

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Keywords: asymmetric catalysis • hydrogenation • iridium • phthalides • P, N ligand

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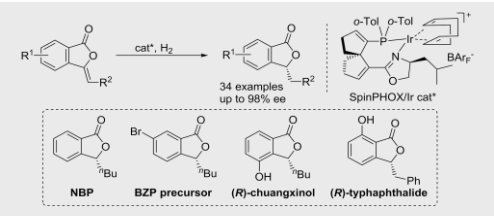

A Shortcut to a wide variety of chiral 3-substituted phthalides with pharmacological interests has been realized by SpinPHOX/Ir catalyzed asymmetric hydrogenation of 3-ylidenephthalides in high enantioselectivities (up to 98% ee).

Yao Ge, Zhaobin Han, Zheng Wang, Chen-Guo Feng, Qian Zhao, Guo-Qiang Lin, and Kuiling Ding**

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Ir-SpinPHOX Catalyzed Enantioselective Hydrogenation of 3-Ylidenephthalides