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Relay Iron/Chiral Brønsted Acid Catalysis: Enantioselective Hydrogenation of Benzoxazinones

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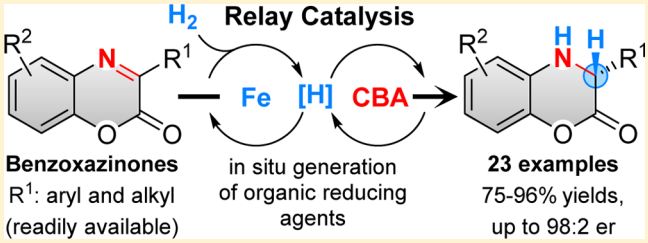
Supporting Information

ABSTRACT: An asymmetric hydrogenation reaction of benzoxazinones has been accomplished via a relay iron/chiral Brønsted acid catalysis. This approach provides a variety of chiral dihydrobenzoxazinones in good to high yields (75−96%) and enantioselectivities (up to 98:2 er). It is noteworthy that challenging 3-alkyl-substituted substrates underwent highly enantioselective reduction. A key to success is the utilization of a nonchiral phosphine ligand to reduce disadvantageous background reactions through tuning the catalytic activity of $Fe_3(CO)_{12}$.



INTRODUCTION

Asymmetric hydrogenation (AH) is arguably one of the most prominent chemocatalytic methods for the synthesis of optically pure organic chemicals.[1] In general, the success of these reactions is attributed to the use of platinum group metals such as Ru, Rh, Ir, and Pd.[1−3] From an environmental and economic viewpoint, it is more desirable to conduct AH reactions with more abundant and cheaper first-row transition metals.[4−7] In the past decade, significant advancements have been witnessed in iron-catalyzed hydrogenations,[5−7] including the corresponding asymmetric processes. In this context, iron complexes with chiral tetradentate ligands were used to efficiently catalyze AH reactions of ketones by the groups of Morris,[6a,d] Berkessel,[6b,c] and Gao.[6e] Besides, in the past years our group developed a cooperative catalysis system by combining the Knölker's iron complex and chiral Brønsted acids (CBA) for the AH reactions of linear and cyclic imines.[7] Despite these improvements, new strategies are still awaited to extend the range of application with respect to iron-catalyzed AH reactions.

Dihydrobenzoxazinone is a ubiquitous scaffold in many biologically active molecules ranging from fungicides and herbicides to drugs.[8] Therefore, many efforts have been made to achieve the synthesis of chiral dihydrobenzoxazinones.[9,10] For example, in 2001 Gorohovky and Bittner first developed a sequence process to efficiently synthesize such molecules using natural amino acids as chiral sources (Figure 1a).[9a] In 2006, Lectka and co-workers reported a highly enantioselective [4 + 2] cycloaddition of *o*-benzoquinone imides with in situ generated ketenes (Figure 1b).[9b,c] Through this route, enantioenriched dihydrobenzoxazinones were conveniently prepared and further applied in the synthesis of amino acid derivatives. In the past decade, catalytic asymmetric reductions

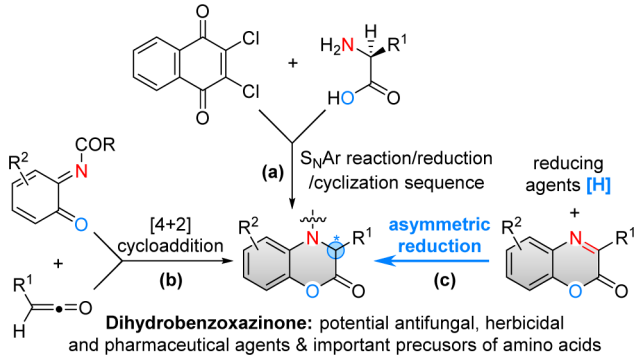


Figure 1. Synthesis of chiral dihydrobenzoxazinones.

have been applied to access the same type of heterocyclic compounds (Figure 1c), too.[10] For instance, in 2006 the groups of MacMillan[10a] and Rueping[10b] independently disclosed the chiral Brønsted acid (CBA)-catalyzed asymmetric transfer hydrogenation (ATH) reaction of benzoxazinones using Hantzsch ester as the stoichiometric reducing reagent. Recently, Zhou and co-workers elegantly achieved the same transformation using catalytic amounts of NAD(P) mimics[11] (i.e., Hantzsch pyridine and phenanthridine). In these works, NAD(P)H mimics are in situ regenerated under hydrogen atmosphere in the presence of a specific ruthenium complex.[10f,g] In 2013, Vidal-Ferran and Núñez-Rico found that iridium complexes with enantiopure phosphine−phosphite ligands efficiently promote the AH reaction of benzoxazinones with high enantioselectivities.[10h] However, these catalytic

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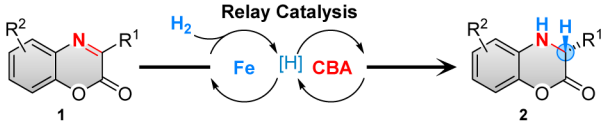
reduction methods suffered from the limited scope of benzoxazinones, and generally only 3-aryl-substituted derivatives can be reduced with good efficiency and high selectivity. Herein, we disclose an AH reaction of benzoxazinones via a relay iron/CBA catalysis (Scheme 1).[12] Through this approach, diverse chiral dihydrobenzoxazinones including demanding 3-alkyl-substituted derivatives are provided in high yields (75−96%) and enantioselectivities (up to 98:2 er).

Scheme 1. Proposal for the AH Reaction of Benzoxazinones via a Relay Iron/CBA Catalysis



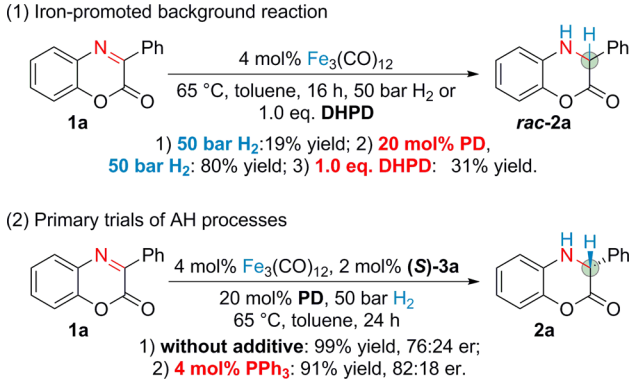
Advantages:
- **Fe:** cheaper, nontoxic and more abundant;
- **H_2:** cheaper, atom-economic and easily available;
- Efficient for 3-alkyl-substituted benzoxazinones.

Challenge:
- **PD** vs substrate **1**: selectivity issue between different imine species.

RESULTS AND DISCUSSION

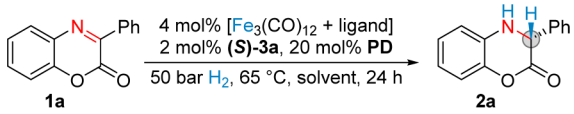
Last year, we found that $Fe_3(CO)_{12}$ can be used to catalyze the reduction of commercially available phenanthridine (**PD**) to NAD(P)H mimics dihydrophenanthridine (**DHPD**) in the presence of H_2,[13] and this method was applied to the hydrogenation of α-keto esters and their derivatives. For example, the introduction of 20 mol % amounts of **PD** to the hydrogenation reaction of benzoxazinone **1a** resulted in a good yield (Scheme 2-1: 80% yield). However, highly enantioselective hydrogenation processes have not yet been realized with this system. A critical challenge that remains for this proposed process is the strong background reaction promoted by $Fe_3(CO)_{12}$,[14] which is erosive to the desired asymmetric ATH process. As illustrated in Scheme 2, benzoxazinone **1a** can be hydrogenated to generate dihydrobenzoxazinone **2a** in 19% yield in the presence of catalytic amounts of $Fe_3(CO)_{12}$ and 50 bar H_2 without **PD**. Meanwhile, $Fe_3(CO)_{12}$ was found to have the ability to catalyze the transfer hydrogenation reaction of **1a** with **DHPD** as the hydride source (Scheme 2-1: 31% yield). We wondered whether diverse catalytic activities of $Fe_3(CO)_{12}$ could be tuned by appropriate ligands, and importantly, these ligands themselves would tolerate well the chiral Brønsted acid in the catalytic cycle of asymmetric transfer hydrogenation.

Scheme 2. Fe-Promoted and Fe-Catalyzed Hydrogenation of 1a



Variation of Conditions. With this idea in mind, the model reaction of benzoxazinone **1a** was investigated in the presence of $Fe_3(CO)_{12}$, **PD**, and (*S*)-**3a** under H_2 atmosphere (50 bar) at 65 °C. As highlighted in Scheme 2, the devised AH reaction gave the desired reduced product **2a** in 99% yield with moderate enantioselectivity (76:24 er). Also, consistent with our hypothesis, the added ligands did affect the reaction efficiency and enantioselectivity. Hence, introducing the phosphine ligand PPh_3 led to an increased enantiomer ratio (82:18 vs 76:24). Encouraged by these results, we further studied the effect of different ligands on the reaction efficiency and enantioselectivity. As shown in Table 1, the introduction of different less-hindered phosphine ligands substantially improved the enantioselectivity (entries 1, 2, 5, 6, and 8). Notably, in the case of electron-rich and bidentate phosphines (entries 1, 5, and 6) high yields and good enantioselectivities were obtained. Meanwhile, the use of excess of phosphine ligands (entry 7), tetradentate ligand (entry 9) or *N*-heterocyclic carbene (entry 10) completely inhibited this reaction.[15]

Table 1. Fe/CBA Relay-Catalyzed AH Reaction of 3-Phenylbenzoxazinone: Ligand Effects[a]



entry	ligand	yield (%)[b]	er[b]
1	TMP	92	84:16
2	P(*p*-F-Ph)$_3$	91	82:18
3	P(*o*-Me-Ph)$_3$	96	77:23
4	P(1-Naph)$_3$	95	78:22
5	PCy_3	92	82:18
6	DPPE	92	84:16
7[c]	DPPE	trace	ND
8	Xantphos	93	83:17
9	P($CH_2CH_2PPh_2$)$_3$	trace	ND
10	Mes-NHC	trace	ND

[a]Reaction conditions: **1a** (0.1 mmol), $Fe_3(CO)_{12}$ (4 mol %), ligand (4 mol %), (*S*)-**3a** (2 mol %), **PD** (20 mol %), 50 bar H_2, 0.2 mL of toluene, 24 h, 65 °C. [b]Yield and er value were determined by GC and chiral HPLC. [c]8 mol % of DPPE was used. TMP: tris(4-methoxyphenyl)phosphane. DPPE: 1,2-bis(diphenylphosphino)ethane. Xantphos: 4,5- bis(diphenylphosphino)-9,9-dimethylxanthene. Mes-NHC: 1,3-dimesityl-1*H*-imidazol-2(3*H*)-ylidene. ND: not determined.

With TMP as the best choice, a survey of chiral Brønsted acids (Figure 2) was carried out to further improve the enantioselectivity of the model system. As highlighted in Table

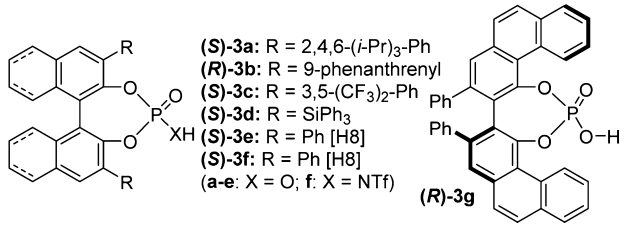


Figure 2. Selected chiral Brønsted acids (**CBA**).

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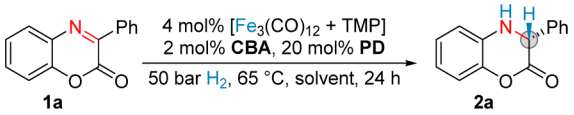
Table 2. Fe/CBA Relay-Catalyzed AH Reaction of 3-Phenylbenzoxazinone: CBA Effects[a]

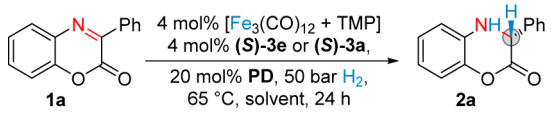


1a 2a

entry	CBA	solvent	yield (%)[b]	er[b]
1	(*S*)-**3a**	0.5 M in toluene	92	84:16
2	(*R*)-**3b**	0.5 M in toluene	35	20:80
3	(*S*)-**3c**	0.5 M in toluene	70	79:21
4	(*S*)-**3d**	0.5 M in toluene	44	68:32
5	(*S*)-**3e**	0.5 M in toluene	78	81:19
6[c]	(*S*)-**3a**	0.5 M in toluene	93	85:15
7[c]	(*S*)-**3e**	0.5 M in toluene	85	84:16
8[c]	(*S*)-**3f**	0.5 M in toluene	87	57:43
9	(*R*)-**3g**	0.5 M in toluene	60	53:47
10[c,d]	(*S*)-**3a**	0.5 M in toluene	38	87:13

[a]Reaction conditions: **1a** (0.1 mmol), $Fe_3(CO)_{12}$ (4 mol %), TMP (4 mol %), **CBA** (2 mol %), **PD** (20 mol %), 50 bar H_2, 0.2 mL of toluene, 24 h, 65 °C. [b]Yields and er values were determined by GC and chiral HPLC. [c]Using 4 mol % of **CBA**. [d]Using 2 mol % of $Fe_3(CO)_{12}$ and 2 mol % of TMP.

Table 3. Fe/CBA Relay-Catalyzed AH Reaction of 3-Phenylbenzoxazinone: Other Effects[a]



1a 2a

entry	[H]	solvent	yield (%)[b]	er[b]
1	**PD**	0.5 M in toluene	85	84:16
2	**2-Me-PD**	0.5 M in toluene	6	56:44
3	**2-Ph-PD**	0.5 M in toluene	7	50:50
4	**10-Me-PD**	0.5 M in toluene	13	84:16
5	**10-*i*Pr-PD**	0.5 M in toluene	11	78:22
6	**4**	0.5 M in toluene	trace	ND
7	**PD**	0.5 M in toluene	93	85:15
8	**PD**	0.1 M in toluene	80	87:13
9	**PD**	0.1 M in CH_2Cl_2	22	76:24
10	**PD**	0.1 M in THF	14	61:39
11	**PD**	0.1 M in AcOEt	58	84:16
12[c]	**PD**	0.1 M in toluene	89	87:13
13[d]	**PD**	0.1 M in toluene	53	88:12
14[e]	**PD**	0.1 M in toluene	43	88:12
15[c,f]	**PD**	0.1 M in mesitylene	91 (88)	91:9

[a]Reaction conditions: **1a** (0.1 mmol), $Fe_3(CO)_{12}$ (4 mol %), TMP (4 mol %), (*S*)-**3e** (4 mol %, entries 1–6) or (*S*)-**3a** (4 mol %, entries 7–15), **PD** or its analog (20 mol %), 50 bar H_2, 0.2 mL of toluene, 24 h, 65 °C. [b]Yields and er values were determined by GC and chiral HPLC. [c]48 h. [d]45 °C. [e]30 bar H_2. [f]Isolated yield in parentheses. ND: not determined.

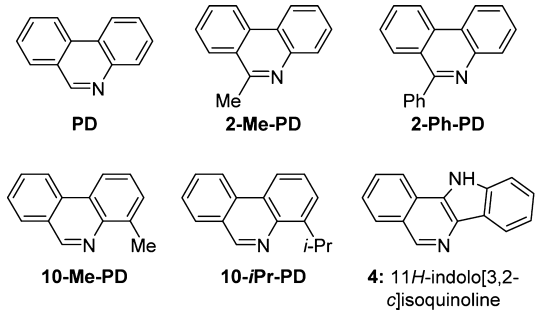


Figure 3. PD and its analogs.

2, both steric and electronic effects of the CBA have a profound influence on the reaction efficiency and selectivity. For example, sterically demanding acids such as (*S*)-**3a** and (*S*)-**3e** (entries 1 and 5) or electron-deficient ones like (*S*)-**3c** and (*S*)-**3f** (entries 3 and 8) promoted the reaction with high yields. Among the different acids, sterically hindered (*S*)-**3a** catalyzed this reaction with better efficiency and selectivity. Besides, increasing the amount of acid catalysts slightly improved the result (entry 6, 93% yield, 85:15 er; entry 7, 85% yield, 84:16 er), while reducing the loading of $Fe_3(CO)_{12}$ and TMP resulted in low reaction efficiency albeit with marginally improved enantioselectivity (entry 10, 38% yield, 87:13 er).

The effect of NAD(P) mimics, **PD** and its analogs (Figure 3), has been also investigated using chiral Brønsted acid (*S*)-**3e**. As highlighted in Table 3, the introduction of methyl, *iso*-propanyl, or phenyl groups into the 2- or 10-postion of **PD** unit resulted in worse reaction efficiency and enantioselectivity (entries 2–5 vs entry 1). Replacing PD with 11*H*-indolo[3,2-*c*]isoquinoline (**4**) completely prevented this AH reaction (entry 6). In order to improve the catalytic performance, further optimization of other reaction parameters such as solvent and concentration was carried out (entries 7–11). We found that diluted solution and low-polarity solvent gave out higher enantioselectivities (entry 8 vs 7; entry 8 vs entries 9–11). Lower temperature or H_2 pressure obviously reduced the reaction efficiency (entries 12 and 13). Prolonging the reaction time can slightly improve the yield (entry 12 vs 7). Finally, the optimal condition was obtained showing high yields and good enantioselectivity (entry 15:91% yield, 90:10 er).[16]

Scope of Benzoxazinones. Next, we examined the generality of AH reaction with respect to 3-aryl substituted benzoxazinones under the Fe/CBA relay catalysis condition. As revealed in Table 4, benzoxazinones including electron-neutral (entry 1, **1a**, 88% yield, 91:9 er), electron-deficient (entry 2, **1b**, 96% yield, 95:5 er), electron-rich (entry 3, **1c**, 75% yield, 92:8 er), and sterically demanding (entry 4, **1d**, 87% yield, 95:5 er) substituents on the aryl ring as well as multiple substituents (entry 5, **1e**, 85% yield, 97:3 er; entry 6, **1f**, 75% yield, 95:5 er) smoothly gave the corresponding products. Generally, prolonged reaction time is required for electron-rich substrates (**1c** and **1f**) in order to obtain good yields. It is noteworthy that for the reactions of all these substrates higher enantiomeric ratios of the corresponding products were observed compared to the model substrate **1a**.

Then, we moved our attention to the asymmetric reduction of more challenging 3-alkyl-substituted benzoxazinones. Remarkably, good to excellent results were obtained for AH reactions of a series of 3-alkyl-substituted substrates by using CBA (*S*)-**3a** or (*S*)-**3d** (Table 5). Although being investigated, only modest results were obtained for reactions of 3-ethyl- and 3-phenylethyl substituted benzoxazinones (**2g**, 27% yield, 89:11 er; **2k**, 96% yield, 54:46 er) in previous reports.[10b,d] Instead, with application of our Fe/CBA relay catalysis system, the same products are easily available with 81% yield, 93:7 er (entry 1) and 88% yield, 97:3 er (entry 5), respectively. Interestingly, this novel catalyst system also tolerates many functional groups such as alkene (**1m**), methoxyl (**1n**), and chloride (**1o**) (entries 7–10) groups. In general, the desired chiral dihydrobenzoxazinones were accessed in good yields (76–89%) and high

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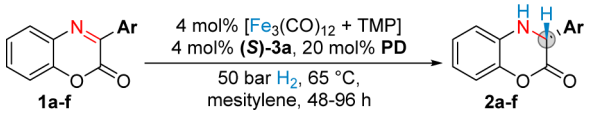
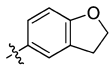
Table 4. Asymmetric Hydrogenation of 3-Aryl-Substituted Benzoxazinones[a]



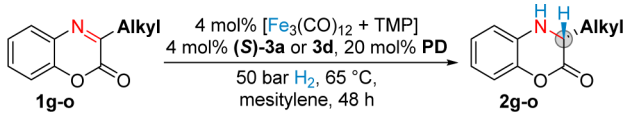
entry	3-aryl	time	yield (%)[b]	er[c]
1	**1a**: Ph	48 h	88	91:9
2	**1b:** 4-F-Ph	48 h	96	95:5
3	**1c:** 4-MeO-Ph	72 h	75	92:8
4	**1d:** 4-*t*-Bu-Ph	48 h	87	95:5
5	**1e:** 3,4-2Me	48 h	85	97:3
6	**1f:** 	96 h	75	95:5

[a]Unless otherwise indicated, all reactions were performed on a 0.2 mmol scale under the optimum conditions as entry 15 in Table 3 for 48–96 h. [b]Isolated yield. [c]Determined by chiral HPLC.

enantioselectivities (93:7–95:5 er). Notably, in the case of 3-alkenyl substituted benzoxazinone **1m**, both (*S*)-**3a** or (*S*)-**3d** were efficient for this transformation (entries 7 and 8), though the former exhibited higher catalytic activity and the latter showed better stereoinduction ability.

Finally, we also investigated the substituent effect on the benzene ring of 3-butyl benzoxazinones. As shown in Table 6, the electronic properties of the substituents have some effect on this reaction. For example, the reactions of benzoxazinones with electron-deficient groups, such as fluorine (**1p**) and chlorine (**1q**), at 7-position exhibited better reactivity than the ones with electron-rich groups (**1r**, **1s**). In the latter cases prolonged time were necessary to obtain good yields. Nevertheless, all tested benzoxazinones were transformed to the desired products with good results (80–91% yields, 92:8–98:2 er).

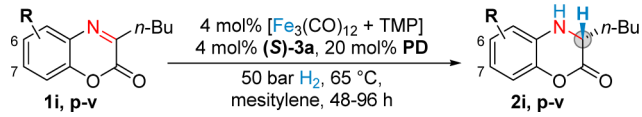
Table 5. Asymmetric Hydrogenation of 3-Alkyl-Substituted Benzoxazinones[a]

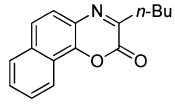


entry	3-alkyl	CBA	yield (%)[b]	er[c]
1	**1g**: Et	(*S*)-**3d**	81	93:7
2	**1h:** *i*-Pr	(*S*)-**3d**	75	94:6
3	**1i:** *n*-Bu	(*S*)-**3a**	91	98:2
4	**1j**: Bn	(*S*)-**3d**	89	95:5
5	**1k:** 	(*S*)-**3d**	88	97:3
6	**1l:** 	(*S*)-**3a**	94	94:6
7	**1m:** 	(*S*)-**3a**	85	93:7
8[d]	**1m:**	(*S*)-**3d**	76	95:5
9	**1n:** 	(*S*)-**3d**	89	94:6
10	**1o:** 	(*S*)-**3d**	84	95:5

[a]Unless otherwise indicated, all reactions were performed on a 0.2 mmol scale under the optimum conditions as entry 15 in Table 3 for 48 h. [b]Isolated yield. [c]Determined by chiral HPLC or GC. [d]96 h.

Table 6. Hydrogenation of Aryl-Substituted 3-Butyl-Benzoxazinones[a]

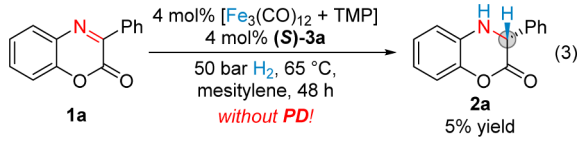


entry	R	time	yield (%)[b]	er[c]
1	**1i**: H	48 h	91	98:2
2	**1p**: 7-F	48 h	83	94:6
3	**1q:** 7-Cl	48 h	81	94:6
4	**1r:** 7-Me	72 h	86	96:2
5	**1s:** 7-MeO	72 h	84	92:8
6[d]	**1t:** 6-Me	90 h	83	95:5
7	**1u**: 5-Me	72 h	86	98:2
8	**1v:** 	72 h	80	94:6

[a]Unless otherwise indicated, all reactions were performed on a 0.2 mmol scale under the optimum conditions as entry 15 in Table 3 for 48–90 h. [b]Isolated yield. [c]Determined by chiral HPLC. [d](*S*)-**3d** was used.

Mechanism Analysis. As shown in Scheme 3, we propose an iron/CBA relay catalysis mechanism for this hydrogenation reaction of benzoxazinones. In cycle I, the organic reductant **DHPD** is generated from **PD** in the presence of a catalytic amount of $Fe_3(CO)_{12}$ and molecular hydrogen. Then, an asymmetric transfer hydrogenation undergoes selective reduction of the benzoxazinone by **DHPD** with the help of the chiral Brønsted acid. In the second cycle, the chiral Brønsted acid is responsible for the control of enantioselectivity through the possible synergetic hydride transfer process (Figure 4).[10g] The observed high selectivity is likely a result of the following: (1) the good stereoinduction ability of **CBA** itself (**CBA** catalysis), and (2) the suppression of the unfavorable background reactions (Fe-catalyzed direct hydrogenation with H_2 and the transfer hydrogenation with **DHPD**).

Two control experiments were implemented to support the proposed pathway: (1) In the absence of organic mediator **PD**, the AH reaction gave the reduction product in very low yield (eq 3). (2) In the absence of iron catalyst and phosphine



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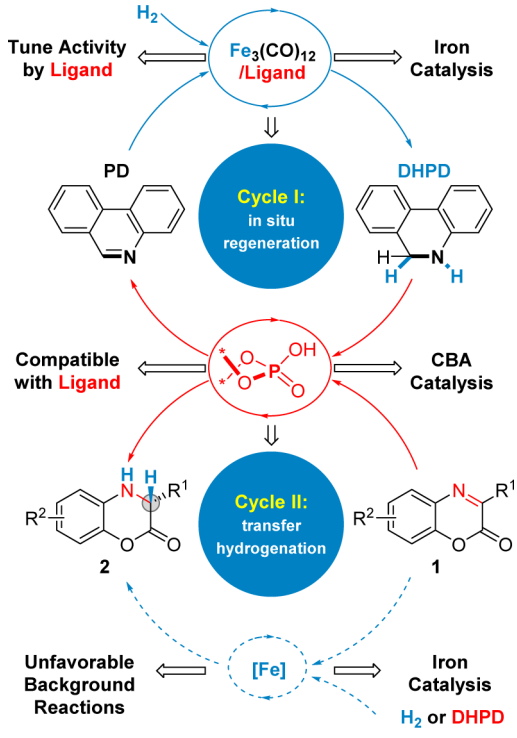
Scheme 3. Proposed Mechanism of the Relay Fe/CBA Catalysis Process



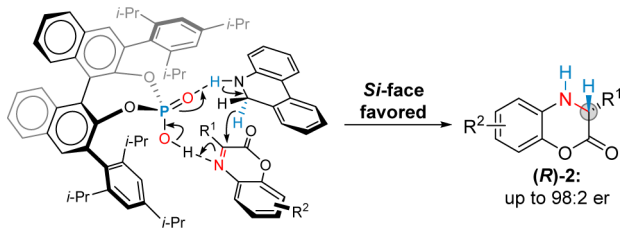
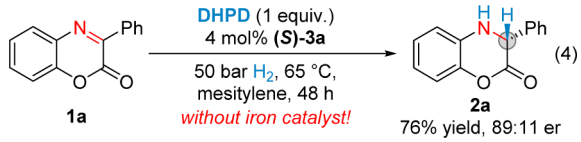


Figure 4. Proposed model for the enantioinduction resulting from the synergetic hydride transfer process.

ligand, the direct transfer hydrogenation with stoichiometric **DHPD** delivered the product **2a** in a slightly decreased yield and similar enantioselectivity (eq 4, 76% yield and 89:11 er).



These results ruled out the possibility that the chiral iron species derived from $Fe_3(CO)_{12}$ and **CBA** could promote the AH reaction of benzoxazinones without the process of **CBA**-catalyzed transfer hydrogenation (cycle II in Scheme 2).

CONCLUSION

In conclusion, we have developed the first example of Fe/CBA relay-catalyzed asymmetric hydrogenations of benzoxazinones. This reduction methodology delivers interesting chiral building blocks from easily available starting materials in good to excellent isolated yields and enantioselectivities. It is noteworthy that 3-alkyl-substituted benzoxazinones are more selectively reduced compared to previous reported methods. The present methodology makes use of a simple iron carbonyl complex and proceeds with molecular hydrogen, which makes the overall process more atom-efficient compared to transfer hydrogenations. A key to success is the utilization of a suitable nonchiral phosphine ligand, which tunes the catalytic activity of the iron carbonyl complex and decreases unselective background reductions. Further applications of this type of catalysis are currently under way.

METHODS

General Procedure for Hydrogenation. Under the atmosphere of Ar, benzoxazinone (0.2 mmol), phenanthridine **3b** (7.2 mg, 0.04 mmol), tris(4-methoxy-phenyl)-phosphine (2.8 mg, 0.008 mmol), $Fe_3(CO)_{12}$ (4.0 mg, 0.008 mmol), mesitylene (2.0 mL), chiral phosphate (*S*)-**3a** (6.0 mg, 0.008 mmol) or (*S*)-**3d** (6.9 mg, 0.008 mmol), and a magnetic stirrer were placed in a reaction vial, which was then capped with a septum equipped with a syringe needle. After stirring for 15 min, the vials together with an alloy plate were placed in the predried autoclave. Once sealed, the autoclave was purged three times with H_2, and then pressurized to 50 bar and heated at 65 °C for 48−96 h. Then, the autoclave was cooled to room temperature and depressurized. The reaction mixture was purified by column chromatography on silica gel (eluent: *n*-hexane/ethyl acetate 10:1−8:1) to give the corresponding chiral product **2**. The enantiomer ratios were determined by Chiral HPLC or GC.

ASSOCIATED CONTENT

Supporting Information

Additional experimental results, procedures, and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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