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Cooperative Iron–Brønsted Acid Catalysis: Enantioselective Hydrogenation of Quinoxalines and 2*H*-1,4-Benzoxazines

Steffen Fleischer,[a] Shaolin Zhou,[b] Svenja Werkmeister,[a] Kathrin Junge,[a] and Matthias Beller*[a]

Chiral six-membered nitrogen heterocycles, such as substituted piperazines, morpholines and piperidines, are found in many naturally occurring alkaloids as well as in pharmaceuticals and constitute an integral part of numerous important bioactive compounds.[1] The biological and pharmacological properties of their aryl-fused analogues tetrahydroquinoxaline and dihydro-2*H*-benzoxazine have been known for a long time. As early as 1947 various tetrahydroquinoxalines have already been synthesised to explore antimalarial activity,[2] whereas the antituberculouses properties of dihydrobenzoxazines have been shown only ten years later.[3]

Since then, interest in tetrahydroquinoxalines and dihydro-2*H*-benzoxazines has increased significantly and today optically active 2-substituted 1,2,3,4-tetrahydroquinoxalines[4] and 3-substituted 3,4-dihydro-2*H*-1,4-benzoxazines[5] constitute interesting building blocks in the drug discovery process and are an important motif of many naturally occurring alkaloids (Figure 1). More specifically, the chiral 1,2,3,4-tetrahydroquinoxaline A is a promising M2 acetylcholine receptor inhibitor,[6] whereas B has been pursued as a potent V2 receptor antagonist.[7] In addition, C is known to represent an active cholesteryl ester transfer protein inhibitor[8] and the chiral 1,4-benzoxazine D is a promising candidate in atherosclerosis treatment.[9] Levofloxacin is a commercialised highly potent antibacterial agent[10] and obscurinervine and its related compounds are examples for naturally accruing alkaloids.[11]

With the growing importance of such chiral compounds in the life science industries, the development of efficient enantioselective methodologies continues to be interesting for organic chemistry and catalysis. Clearly, beside different multistep methods to synthesise chiral tetrahydroquinoxalines[12] and dihydro-benzoxazines[13] the most direct and atom-economic approach represents the enantioselective hydrogenation of quinoxalines and benzoxazines. Notably, virtually all of the known catalysts for the latter enantioselective hydrogenation are based on noble metals such as Ru, Rh and Ir.[14,15] Owing to the comparably high price of these precious metals and their limited availability the search for more economical and environmentally friendly catalysts based on Zn, Cu and Fe offers particular attractive options.[16–18] However, despite obvious advantages enantioselective hydrogenations based on these metals remain an underrepresented field. To the best of our knowledge, no reports of enantioselective hydrogenations of quinoxalines and benzoxazines by using non-noble metal catalysts are known.

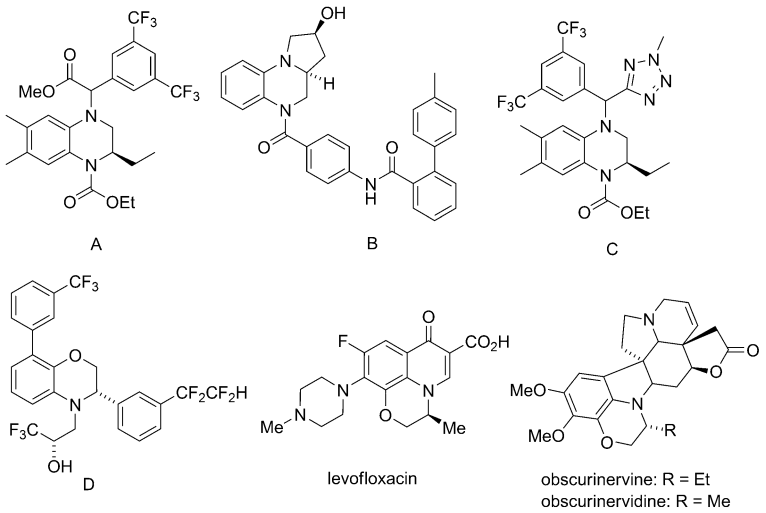

Figure 1. Selection of bioactive compounds and alkaloids containing tetrahydroquinoxaline and dihydro-2*H*-1,4-benzoxazine frameworks.

[a] S. Fleischer, S. Werkmeister, Dr. K. Junge, Prof. Dr. M. Beller
Leibniz-Institut für Katalyse e.V. an der Universität Rostock
Albert-Einstein-Straße 29a, 18059 Rostock (Germany)
Fax: (+49) 381-1281-5000
E-mail: matthias.beller@catalysis.de

[b] Dr. S. Zhou
College of Chemistry, Central China Normal University
Luoyu Road, No. 152, 430079 Wuhan (P.R. China)

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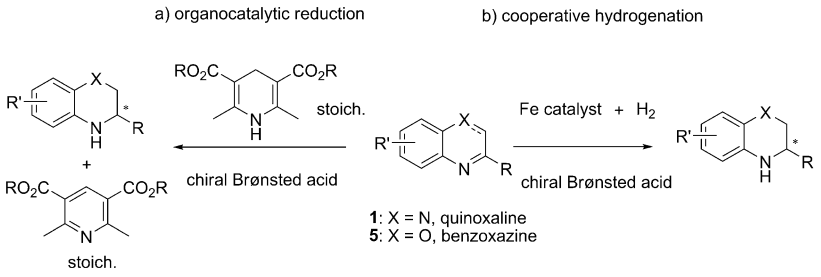
Only recently, non-noble metal catalysts were reported for the homogeneous enantioselective hydrogenation of ketones and simple imines. For example, the hydrogenation of C=O bonds based on Cu catalysts was reported by Shimizu et al.[18a–d] and our group.[18e] In 2008, Morris et al.[19] reported the first enantioselective hydrogenation of acetophenone applying an Fe-based complex with a tetradentate PNNP ligand. Furthermore, Berkessel and co-workers[20] used phosphoramidate ligands to form chiral Fe complexes for the enantioselective hydrogenation of acetophenone.

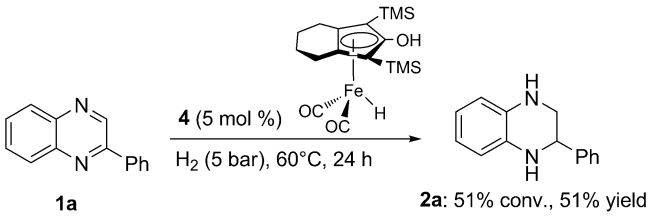
An alternative but highly selective approach has been reported by Rueping et al., List et al., MacMillan et al., and Antilla and co-workers, which use chiral Brønsted acids as organocatalysts for the enantioselective reduction of C=N bonds.[21] Notably, the research group of Rueping applied this methodology in the highly enantioselective reduction of 2-aryl-quinoxalines and 3-aryl-benzoxazines by using chiral Brønsted acids as organocatalysts.[21a,j] Unfortunately, in all these reactions stoichiometric amounts of expensive 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylates (Hanztsch esters) have to be applied as the hydrogen source and the formation of pyridines as co-products limited the application of this methodology (Scheme 1).



Scheme 1. a) Organocatalytic reduction and b) cooperative enantioselective Fe-catalysed hydrogenation of quinoxalines **1** and 2*H*-1,4-benzoxazines **5**.

Based on our recent work on the cooperative iron-catalysed hydrogenation of imines we report here a highly selective asymmetric hydrogenation of various nitrogen heterocycles (Scheme 1).[22] The combination of a molecularly defined achiral Fe-hydrogenation catalyst with a chiral Brønsted acid allows for the enantioselective reduction of various 2-substituted quinoxalines and 3-substituted 1,4-benzoxazines with environmentally friendly hydrogen gas to form the corresponding chiral tetrahydroquinoxalines and dihydro-2*H*-1,4-benzoxazines in high yields up to 97% with excellent enantiomeric ratios (e.r.) up to 97:3.

For our initial studies the hydrogenation of 2-phenylquinoxaline (**1a**) was chosen as a benchmark reaction. The achiral Fe complex **4**, which was synthesised according to the work of Knölker and co-workers,[23] was able to hydrogenate both C=N double bonds of **1a** and racemic **2a** was obtained with 51% yield under non-optimised conditions (Scheme 2).[24] Notably, this reaction represents the first example of an Fe-catalysed hydrogenation of quinoxalines.



Scheme 2. Hydrogenation of compound **1a** with the Fe-based catalyst **4**. TMS = trimethylsilyl.

Due to the importance of chiral 1,2,3,4-tetrahydroquinoxalines our following studies concentrated on expanding this protocol towards an enantioselective version. As chiral 1,1′-binaphthalene-2,2′-diol (binol) phosphoric acid esters showed high selectivity in the enantioselective reduction of C=N bonds by using Hanztsch ester as reducing agent, we thought that the proper choice of the chiral phosphoric acid esters **3** will control the enantioselectivity of the hydrogenation. Although the latter acid **3** has to activate specifically substrate **1a**, the former Fe-based hydrogenation catalyst **4** has to react with the activated intermediate to perform the cooperative hydrogenation.

To our delight, the combination of catalyst **4** with various chiral 3,3′-biaryl-1,1′-binaphthyl-2,2′-diyl hydrogen phosphates (**3a**–**3e**), two H_8-binaphthyl analogous (**3g** and **3h**) and (*R*)-2,2′-diphenyl-3,3′-biphenanthryl-4,4′-diyl phosphate (VAPOL hydrogenphosphate, **3f**) created active catalysts for the enantioselective hydrogenation of **1a** (Table 1, entries 1–8). The different substituents at the 3- and 3′-position of **3a**–**3e** as well as **3g** and **3h** had only a little impact on the product yield (67–99%), whereas a significant influence on the enantiomeric ratios was observed (54:46 to 95:5). Without any substituents at the 3- and 3′-position, only low enantioselectivity occurred (Table 1, entry 2). Sterically demanding aryl substituents led to an increased enantioselectivity (Table 1, entries 1, 4, and 5), whereas the best results were obtained by using bi- and tricyclic moieties (Table 1, entries 3, 7 and 8). Notably, chiral Brønsted acids with axial *R* configuration yielded product **2a** with *S* configuration and vice versa (Table 1, entries 1–8).

Under the model conditions the Brønsted acid **3c** in combination with the Fe complex **4** allows for the smooth hydrogenation of the heterocyclic core giving 2-phenyl-1,2,3,4-tetrahydroquinoxaline (**2a**) in high yield of 87% and an excellent enantiomeric ratio of 95:5 (Table 1, entry 3). Important to note, the level of enantioselectivity observed with an iron precursor rivals those of the most efficient precious-metal-based hydrogenations as well as organocatalytic transfer hy-

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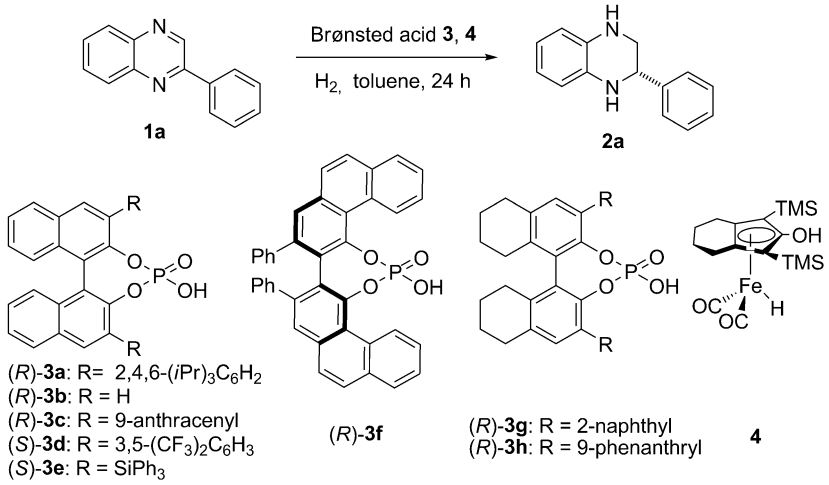
Table 1. Enantioselective Fe-catalysed hydrogenation of **1a** in the presence of various chiral Brønsted acids **3**.[a]



Entry	Brønsted catalyst **3** ([mol%])	T [°C]	p [bar]	Yield[b] [%]	e.r. (*S*):(*R*)-**2a**[c]
1	(*R*)-**3a** (2)	40	20	99	86:14
2	(*R*)-**3b** (2)	40	20	74	54:46
3	**(*R*)-3c (2)**	**40**	**20**	**87**	**95:5**
4	(*S*)-**3d** (2)	40	20	85	26:74
5	(*S*)-**3e** (2)	40	20	75	19:81
6	(*R*)-**3f** (2)	40	20	67	89:11
7	(*R*)-**3g** (2)	40	20	75	92:8
8	(*R*)-**3h** (2)	40	20	81	90:10
9	(*R*)-**3c** (2)	40	5	81	95:5
10	(*R*)-**3c** (2)	40	40	80	95:5
11	(*R*)-**3c** (2)	60	5	98	94:6
12	(*R*)-**3c** (1)	60	5	98	94:6
13[d]	**(*R*)-3c (1)**	**60**	**5**	**93**	**94:6**
14[e]	–	60	5	–	n.d.
15[f]	**(*R*)-3c (1)**	60	5	–	n.d.

[a] Reaction conditions: **1a** (0.5 mmol), Brønsted acid **3** (1–2 mol%), Fe catalyst **4** (5 mol%), toluene (1 mL), H_2 (5–40 bar) at 40–60°C for 24 h. [b] The yield was determined by GC analysis by using hexadecane as an internal standard. [c] The e.r. value was determined by HPLC on a chiral stationary phase. [d] Complex **4** (3 mol%). [e] Reaction was performed without **3** and **4**. [f] Reaction was performed without **4**.

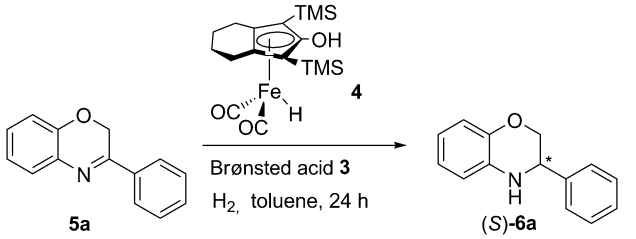
drogenations by using stoichiometric amounts of Hanztsch esters.[25]

Next, the influence of critical reaction parameters such as temperature, pressure and catalyst loading were investigated (Table 1, entries 9–15). A study of the dependence on the hydrogen pressure showed that it has little influence on both yield and enantioselectivity. Hence, lowering the hydrogen pressure from 40 to 5 bar did not lower the yield and the enantiomeric ratio stays as high as 95:5 (Table 1, entry 9 and 10). Increasing the temperature to 60°C at 5 bar hydrogen pressure led to full conversion and **2a** was obtained in 98% yield with an enantiomeric ratio of 94:6 (Table 1, entry 11). We were pleased to see that under these conditions the reaction of **1a** was efficiently catalysed at low catalyst loading of 1 and 3 mol% for **3c** and **4**, respectively (Table 1, entry 13). In order to ensure that the observed catalyst activity was not caused by other metal impurities present, we performed each reaction in brand new glass vials and with new stirring bars.[26] Furthermore, control experiments without any catalyst (Table 1, entry 14) and without Fe complex **4** (Table 1, entry 15) did not show any product formation, which confirms the catalytic effect of the Fe species.

During the further course of our studies we decided to extend our enantioselective hydrogenation procedure to incorporate benzoxazines to form biologically important chiral 3,4-dihydro-2*H*-1,4-benzoxazines. To our delight, also this reactions proceed with good enantioselectivity (Table 2). However, in contrast to the hydrogenation of quinoxalines, the best enantiomeric ratio of 83:17 was observed by applying **3a** as chiral Brønsted acid (Table 2, entry 1).

Once suitable catalyst systems were identified, the scope and limitations of our novel iron-catalysed enantioselective hydrogenation by using different 2-substituted quinoxalines as substrates were explored. A variety of quinoxalines with aromatic, heteroaromatic, cyclic and aliphatic substituents at the heteroaromatic core and different substituents at the 6- and 7-position were hydrogenated smoothly with high yields up to 97% and good to excellent enantiomeric ratios up to 97:3 (Table 3, entries 1–14). Both electron-donating and electron-withdrawing substituents on the aromatic rings at *meta* or *para* position had little impact on the hydrogenation activity and high enantioselectivity is observed for *meta*- and *para*-substituted 2-aryl-quinoxalines (Table 3, entries 1–8). Gratifyingly, substituents at the 6- and 7-position are tolerated (Table 3,

Table 2. Evaluation of the chiral Brønsted acids **3** for the enantioselective hydrogenation of benzoxazines.[a]



Entry	Brønsted catalyst **3** ([mol%])	e.r. (*S*):(*R*)-**2a**[b]
1	**(*R*)-3a (2)**	**87:13**
2	(*R*)-**3b** (2)	52:48
3	(*R*)-**3c** (2)	66:33
4	(*S*)-**3d** (2)	45:55
5	(*S*)-**3e** (2)	47:53

[a] Reaction conditions: **5a** (0.5 mmol), Brønsted acid **3** (2 mol%), Fe catalyst **4** (5 mol%), toluene (1 mL), H_2 (5 bar) at 60°C for 24 h. [b] The e.r. value was determined by HPLC on a chiral stationary phase.

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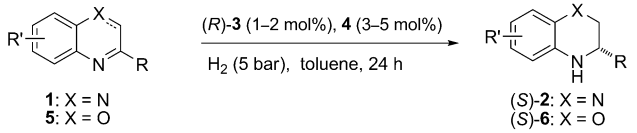
Table 3. Cooperative Fe-catalysed enantioselective hydrogenation of quinoxalines **1** and benzoxazines **5**.



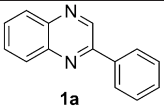
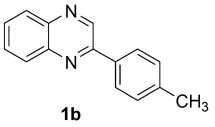
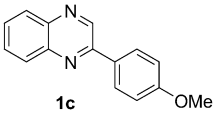
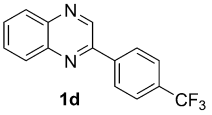
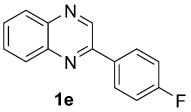
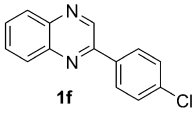
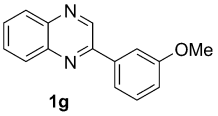
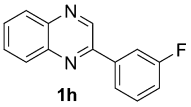
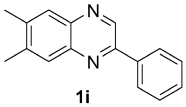
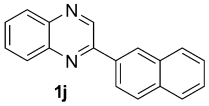
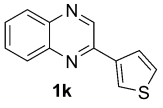
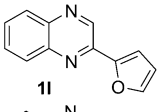
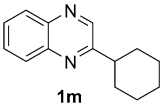
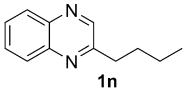
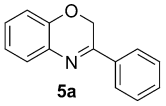
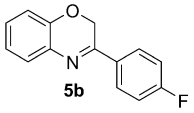
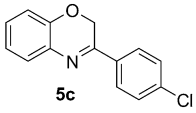
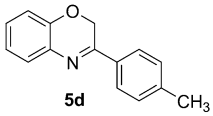
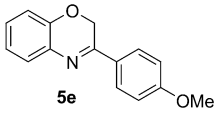
Entry	Imine	Product	Yield[b] [%]	e.r. (*S*)-**2**/(*S*)-**6**[d]
1	 **1a**	**2a**	90	94:6
2	 **1b**	**2b**	82	92:8
3	 **1c**	**2c**	95	91:9
4	 **1d**	**2d**	91	92:8
5	 **1e**	**2e**	91	94:6
6	 **1f**	**2f**	91	94:6
7	 **1g**	**2g**	83	95:5
8	 **1h**	**2h**	91	94:6
9	 **1i**	**2i**	80	88:13
10	 **1j**	**2j**	97	97:3
11	 **1k**	**2k**	96	94:6
12	 **1l**	**2l**	95	80:20
13	 **1m**	**2m**	94	88:12

Table 3. (Continued)

Entry	Imine	Product	Yield[b] [%]	e.r. (*S*)-**2**/(*S*)-**6**[d]
14	 **1n**	**2n**	94	83:17
15	 **5a**	**6a**	90	87:13
16	 **5b**	**6b**	74	84:16
17	 **5c**	**6c**	67	80:20
18	 **5d**	**6d**	76	80:20
19	 **5e**	**6e**	69	79:21

[a] General reaction conditions for quinoxalines: **1** (0.5 mmol), Brønsted acid **3c** (1 mol%), Fe catalyst **4** (3 mol%), toluene (1 mL), H_2 (5 bar) at 60°C for 24 h; for benzoxazines: **5** (0.5 mmol), Brønsted acid **3a** (2 mol%), Fe catalyst **4** (5 mol%), toluene (1 mL), H_2 (5 bar) at 60°C for 24 h. [b] Yield of the isolated product after column chromatography [c] The e.r. value was determined by HPLC on a chiral stationary phase. [d] Complex **4** (3 mol%).

entry 9) and 2-(naphthalen-2-yl)quinoxaline (**1j**) was reduced with excellent yield and enantiomeric ratio (Table 3, entry 10).

As heteroaromatic compounds play an important role in the life science industries we draw our attention towards heteroaromatic substituents. 2-(Thiophen-3-yl)quinoxaline (**1k**) and 2-(furan-2-yl)quinoxaline (**1l**) were again hydrogenated with excellent yields and good to high enantiomeric ratios (Table 3, entries 11 and 12).

We were also interested, if alkyl-substituted quinoxalines can be applied with our catalyst system, too. In contrast to organocatalytic systems applying Hanztsch esters as reducing agents the reduction of alkyl-substituted substrates is achieved with high yield and good enantioselectivity (Table 3, entries 13 and 14).[21]

Furthermore, different benzoxazines can be reduced with the Fe complex **4** and **3a** as chiral Brønsted acid. As expected, the sense of the absolute configuration of product **6** is again *S*, which shows that the configuration is not influenced by the heteroatom X. For **6a**–**6e** enantiomeric ratios up to 87:13 are obtained, which is slightly lower compared to the hydrogenation of **1** with **3c** (Table 3, entries 15–19).

Finally, we wanted to improve the step economy for the synthesis of chiral quinoxalines. Here, our aim was to use commercially available starting materials and to synthesise

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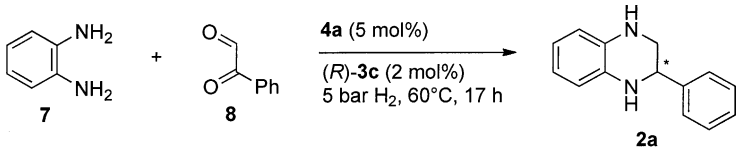
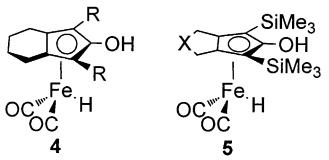
chiral quinoxalines in a one-step procedure, which has not been reported so far. In order to do so, we combined commercially available glyoxal and 1,2-phenylenediamine, which form quinoxaline in a condensation reaction. The resulting quinoxaline might then be enantioselectively reduced in situ to the corresponding chiral tetrahydroquinoxaline. In this reductive amination procedure water is the only byproduct formed.

Following our concept, 1,2-phenylenediamine (**7**) and phenylglyoxal (**8**) were reacted in toluene in the presence of six different iron-based hydrogenation catalysts **4a**–**4d**, **5a** and **5b** and **3c** as the chiral Brønsted acid (Scheme 3). To our delight all iron complexes **4a**–**4d** as well as **5a** and **5b** yield-





4a, R = $SiMe_3$:	**75%, 95:5 e.r.**
4b, R = $Si(^iPr)Me_2$:	96%, 92:8 e.r.
4c, R = $SiCyMe_2$:	86%, 92:8 e.r.
4d, R = $SiEt_3$:	92%, 92:8 e.r.
5a, X = CH_2:	90%, 92:8 e.r.
5b, X = O:	90%, 92:8 e.r.

Scheme 3. Reductive amination procedure to produce **2a**.

ed the chiral tetrahydroquinoxaline **2a** in good yield and high enantioselectivity. Complex **4a** showed the best results giving **2a** in 75% yield and an enantiomeric ratio of 95:5. Remarkably, no drop in enantioselectivity was observed compared to the hydrogenation of the isolated quinoxaline **3a** (Table 1, entry 3).

Comparison of our iron-based system to well established Ru, Rh and Ir hydrogenation catalysts in combination with chiral Brønsted acids[27] proved some activity of the catalysts of Shvo, $[\{Ru(p\text{-cymene})I_2\}_2]$ and $[\{Rh(cod)Cl\}_2]$ (cod = cyclooctadiene) in combination with the chiral Brønsted acid **3c** in the reductive amination of 1,2-phenylenediamine (**7**) and phenylglyoxal (**8**) (see the Supporting Information). However, the catalyst of Shvo yielded **2a** only as a racemic mixture. Notably, applying $[\{Ru(p\text{-cymene})I_2\}_2]$, which was used by Zhou et al. in the enantioselective reduction of quinoxalines,[14h] or $[\{Rh(cod)Cl\}_2]$, in both cases **2a** was obtained with an enantiomeric ratio of 90:10.

In conclusion, we demonstrate here for the first time the enantioselective hydrogenation of quinoxalines and benzoxazines without precious metal catalysts and chiral ligands. Instead, the combination of an Fe based complex with chiral acids allows for smooth hydrogenation with enantiomeric ratios up to 97:3. Employing hydrogen gas as the reductant makes this transformation an ideal atom-economical process. Moreover, for the first time the direct synthesis of chiral tetrahydroquinoxalines through reductive amination was achieved with a high enantiomeric ratio of 95:5. Further studies towards the extension of this strategy to other synthetically interesting compounds are in progress in our laboratory.

Experimental Section

Typical procedure for the enantioselective hydrogenation of quinoxalines 1: Under an argon atmosphere (glovebox), a brand new glass vial was charged with **1** (0.5 mmol), (*R*)-**3c** (0.005 mol), complex **4** (0.015 mmol), toluene (1.5 mL) and a magnetic stirring bar. The glass vial was capped with a septum equipped with a syringe. The vial was placed in the alloy plate, which was then placed to the predried autoclave. Once sealed, the autoclave was purged three times with hydrogen, then pressurised to 5 bar and heated at 60 °C for 24 h. After reaction, the autoclave was cooled to room temperature, depressurised and the reaction mixture was transferred to a flask. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate 10:1) to give the corresponding compound **2**, which was then analysed by NMR spectroscopy, HRMS and chiral HPLC to determine the e.r. value.

Typical procedure for the enantioselective hydrogenation of benzoxazines 5: Under an argon atmosphere (glovebox), a brand new glass vial was charged with **5** (0.5 mmol), (*R*)-**3a** (0.01 mol), complex **4** (0.025 mmol), toluene (1.5 mL) and a magnetic stirring bar. The glass vial was capped with a septum equipped with a syringe. The vial was placed in the alloy plate, which was then placed to the predried autoclave. Once sealed, the autoclave was purged three times with hydrogen, then pressurised to 5 bar and heated at 60 °C for 24 h. After reaction, the autoclave was cooled to room temperature, depressurised and the reaction mixture was transferred to a flask. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate 10:1) to give the corresponding compound **6**, which was then analysed by NMR spectroscopy, HRMS and chiral HPLC to determine the e.r. value.

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[26] Stirring bars were used brand new and used stirring bars were exclusively applied for noble-metal-free reactions and before use cleaned with Aqua regia, water and acetone.

[27] For more details, see the Supporting Information.

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