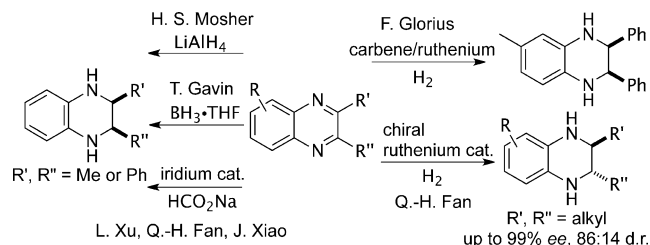


A Highly *cis*-Selective and Enantioselective Metal-Free Hydrogenation of 2,3-Disubstituted Quinoxalines**

Zhenhua Zhang and Haifeng Du*

Abstract: A wide range of 2,3-disubstituted quinoxalines have been successfully hydrogenated with H_2 using borane catalysts to produce the desired tetrahydroquinoxalines in 80–99% yields with excellent *cis* selectivity. Significantly, the asymmetric reaction employing chiral borane catalysts generated by the *in situ* hydroboration of chiral dienes with $HB(C_6F_5)_2$ under mild reaction conditions has also been achieved with up to 96% *ee*, and represents the first catalytic asymmetric system to furnish optically active *cis*-2,3-disubstituted 1,2,3,4-tetrahydroquinoxalines.

Tetrahydroquinoxalines are very useful moieties and present in a wide range of biologically and medicinally active compounds, and a lot of methods have been developed to access them.^[1] The direct reduction of quinoxalines is one of the most efficient approaches among these methodologies.^[2] In particular, the catalytic hydrogenation with H_2 as well as its asymmetric version has attracted attention and great advances have been made.^[3] Since the first asymmetric hydrogenation of 2-methylquinoxaline with chiral rhodium catalysts reported by Murata and co-workers in 1987,^[4a] a variety of chiral transition metal catalysts have been developed for the enantioselective hydrogenation of 2-substituted quinoxalines.^[4] However, in sharp contrast, the reduction of 2,3-disubstituted quinoxalines has been rarely reported.^[5,6] For example, Deselms and Mosher reported a noncatalytic lithium aluminium hydride reduction of 2,3-dimethylquinoxaline to give a *cis* product in 1960 (Scheme 1).^[5a] Gavin and co-workers described the reduction of 2,3-dimethyl- and 2,3-diphenylquinoxaline with borane in THF solution (Scheme 1).^[5b] Recently, Xu, Fan, and Xiao reported an iridium-catalyzed transfer *cis*-selective hydrogenation of 2,3-dimethylquinoxaline (Scheme 1).^[5c] Glorius and co-workers described a ruthenium/carbene-catalyzed *cis*-selective hydrogenation of 2,3-diphenyl-6-methylquinoxaline. In 2011, Fan and co-workers disclosed the first and the only asymmetric hydrogenation of 2,3-dialkylquinoxalines with chiral cationic ruthenium diamine catalysts to give the desired *trans* products



Scheme 1. Reductions of 2,3-disubstituted quinoxalines. THF = tetrahydrofuran.

with up to 99% *ee* and 86:14 d.r. (Scheme 1).^[5c] Therefore, the development of highly stereoselective hydrogenations of 2,3-disubstituted quinoxalines under mild reaction conditions with a good substrate scope, especially the corresponding asymmetric reactions, still remains a challenge in the field of catalytic hydrogenation.

The recently emerging frustrated Lewis pair (FLP) chemistry provides a breakthrough approach for metal-free hydrogenation with molecular H_2 since catalytic hydrogenation has long been dominated by transition-metal catalysis.^[7–9] A wide range of unsaturated compounds have proven to be effective substrates for the FLP-catalyzed hydrogenations.^[9,10] Significantly, some promising advances have also been made for FLP-catalyzed asymmetric reactions,^[11,12] but the asymmetric hydrogenation of silyl enol ethers is the only example to proceed with more than 90% *ee*.^[11f] In 2013, Stephan and co-workers described the hydrogenation of 2,3-dimethyl- and 2,3-diphenylquinoxaline using an equivalent of the Lewis acid $B(C_6F_5)_3$. Interestingly, decahydro- instead of tetrahydroquinoxaline derivatives were obtained.^[10c] As part of our general interest in exploring novel FLP catalytic systems, we recently reported the asymmetric hydrogenation of imines^[11e] and silyl enol ethers,^[11f] and the *cis*-selective hydrogenation of simple pyridines,^[10d] using an *in situ* catalyst generation strategy involving the hydroboration of alkenes with $HB(C_6F_5)_2$ (Piers' borane).^[13,14] Our attempts on other challenging substrates for the hydrogenation show that 2,3-disubstituted quinoxalines can be highly *cis*-selectively and enantioselectively hydrogenated under FLP catalysis. Herein, we report our preliminary efforts on this subject.

Initially, the metal-free hydrogenation of 2,3-dimethylquinoxaline (**1a**) under H_2 (20 bar) at 100°C in toluene was examined using 10 mol % of $B(C_6F_5)_3$ (**3a**)^[15a] or $B(p\text{-}HC_6F_4)_3$ (**3b**).^[15b] These reactions went well to give *trans*-**2a** as a major product (Table 1, entries 1 and 2). Further lowering the temperature can obviously improve the *cis* selectivities (entries 3–6), and up to 98:2 d.r. was obtained at 60°C using **3b**. Reducing the catalyst loading to 5 mol % gave a similar

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Table 1: Hydrogenation of 2,3-disubstituted quinoxalines.^[a]

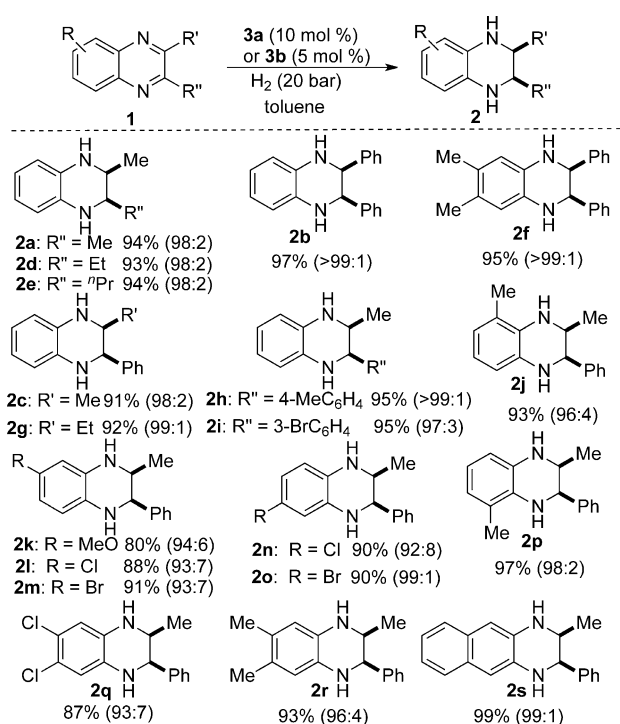
	1a: R' = R'' = Me	3a: B(C ₆ F ₅) ₃	3c: HB(C ₆ F ₅) ₂			
	1b: R' = R'' = Ph	3b: B(<i>p</i> -HC ₆ F ₄) ₃	3d: HB(<i>p</i> -HC ₆ F ₄) ₂			
	1c: R' = Me, R'' = Ph					
Entry	1	3	T [°C]	t [h]	Conv. [%] ^[b]	cis/trans ^[b]
1	1a	3a	100	24	> 99	27:73
2	1a	3b	100	24	> 99	32:68
3	1a	3a	80	20	> 99	63:37
4	1a	3b	80	20	> 99	79:21
5	1a	3a	60	20	> 99	92:8
6	1a	3b	60	20	> 99	98:2
7 ^[c]	1a	3b	60	20	> 99	98:2
8	1b	3a	100	24	> 99	> 99:1
9	1b	3b	100	24	95	> 99:1
10	1b	3c	100	24	48	> 99:1
11	1b	3d	100	24	21	> 99:1
12 ^[c]	1b	3a	100	24	75	> 99:1
13	1b	3a	80	24	85	> 99:1
14	1c	3a	100	20	> 99	92:8
15	1c	3a	60	20	> 99	98:2
16	1c	3a	40	20	83	> 99:1

[a] All reactions were carried out with 2,3-disubstituted quinoxalines (0.10 mmol), borane (10 mol %), and H₂ (20 bar) in toluene (0.5 mL) unless otherwise noted. [b] Determined by ¹H NMR spectroscopy of the crude reaction mixture. [c] 5 mol % of borane was used.

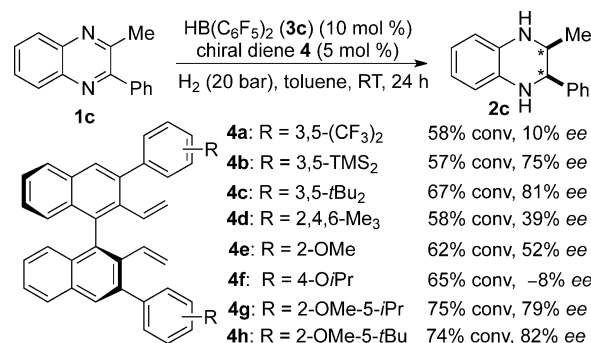
result without loss of any reactivity and selectivity (entry 7). For the hydrogenation of 2,3-diphenylquinoxaline (**1b**), *cis*-tetrahydroquinoxaline (**2b**) was obtained as an exclusive product using the boranes **3a–d**. The borane **3a** gave a quantitative conversion, but **3c**^[13] and **3d**^[15c] gave a much lower conversion (entries 8–13). The borane **3a** was also an efficient catalyst for the hydrogenation of 2-methyl-3-phenylquinoxaline (**1c**), and a quantitative conversion with 98:2 d.r. was afforded at 60 °C (entries 14 and 15). Further decreasing the temperature to 40 °C gave better *cis* selectivity but a lower reactivity (entry 16).

With the optimal reaction conditions in hand, a variety of 2,3-disubstituted quinoxalines were subjected to this metal-free hydrogenation using either **3a** or **3b** as the catalyst. As shown in Scheme 2, different types of substituents at the 2- and 3-positions of quinoxalines are all well tolerated to give the desired products **2a–i** in 91–97 % yields with d.r. values of 98:2–> 99:1. Moreover, 2-phenyl-3-methylquinoxalines bearing different substituents were also effective substrates for furnishing the products **2j–s** in 80–99 % yields with d.r. values of 92:8–99:1.

After achieving the highly *cis*-selective hydrogenation of 2,3-disubstituted quinoxalines, its asymmetric version was next investigated using chiral borane catalysts generated in situ by the hydroboration of chiral dienes with the borane **3c**. As shown in Scheme 3, several chiral dienes (**4a–h**)^[16] were subjected to the asymmetric hydrogenation of the quinoxaline **1c** at room temperature. It was found that all these reactions can furnish *cis*-**2c** as the exclusive product, but substituents at the 3,3'-positions of the binaphthyl framework



Scheme 2. Stereoselective hydrogenation of 2,3-disubstituted quinoxalines: a) dialkylquinoxalines, **3b** (5 mol %), 60 °C; b) diarylquinoxalines, **3a** (10 mol %), 100 °C; c) 2-aryl-3-alkylquinoxalines, **3a** (10 mol %), 60 °C.



Scheme 3. Evaluation of chiral dienes for hydrogenation of the quinoxaline **1c**.

had an influence on the enantioselectivities. The chiral diene **4h** gave a better *ee* value.

The reaction conditions were further optimized. As shown in Table 2, solvents were found to have an obvious impact on both reactivity and enantioselectivity (entries 1–7). Using *n*-hexane as solvent, *cis*-**2c** can be obtained in 89 % conversion with 88 % *ee* (entry 6). Moreover, the reaction concentration can also affect the enantioselectivity, and 89 % *ee* was obtained at a concentration of 0.067 M (entries 8–11). Reducing the catalyst loading to 5 mol % resulted in low conversion and *ee* value (entry 12).

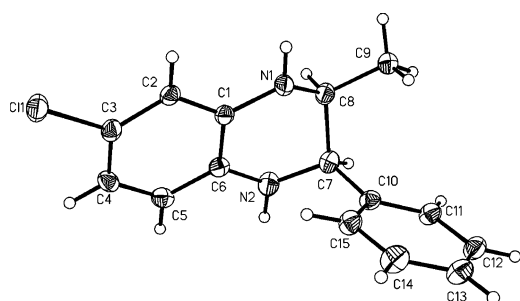
A variety of 2,3-disubstituted quinoxalines were subsequently examined for the metal-free asymmetric hydrogenation in *n*-hexane under H₂ (20 bar) using **4h** (5 mol %) and

Table 2: Optimization of the asymmetric hydrogenation.^[a]

Entry	Solvent	Conc [M]	Conv [%] ^[b]	cis/trans ^[c]	Ee [%] ^[c]
1	toluene	0.1	74	> 99:1	82
2	mesitylene	0.1	60	95:5	80
3	benzene	0.1	87	> 99:1	84
4	CH ₂ Cl ₂	0.1	91	> 99:1	84
5	Et ₂ O	0.1	trace	–	–
6	n-hexane	0.1	89	> 99:1	88
7	cyclohexane	0.1	56	> 99:1	77
8	n-hexane	0.4	91	> 99:1	80
9	n-hexane	0.2	89	> 99:1	82
10	n-hexane	0.067	87	> 99:1	89
11	n-hexane	0.05	82	> 99:1	87
12 ^[d]	n-hexane	0.5	45	> 99:1	76

[a] All reactions were carried out with **1c** (0.10 mmol), HB(C₆F₅)₂ (10 mol%), chiral diene **4h** (5 mol%), and H₂ (20 bar) at room temperature. [b] Determined by ¹H NMR spectroscopy of the crude reaction mixture. [c] Determined by HPLC using a Chiralcel OD-H column. [d] 5 mol% of catalyst.

HB(C₆F₅)₂ (10 mol%). As shown in Table 3, all these reactions proceeded efficiently to furnish the desired tetrahydroquinoxaline products in 71–99% yields with d.r. values of 98:2–> 99:1, and 67–96% ee (entries 1–14). The substituents at the 2,3-positions of the quinoxalines influenced the enantioselectivity (entries 1–4). When 2-phenyl-3,5-dimethylquinoxaline was employed as a substrate, only 67% ee was obtained (entry 5). In contrast, substituents at the 6-, 7-, and 8-positions gave much higher ee values (entries 6–14). The absolute configuration of the compound **2l** was determined to be (2*R*,3*S*) by its X-ray structure (Figure 1).^[17] However, 2,3-dialkyl- and diaryl-substituted quinoxalines were not suitable


Figure 1. X-ray structure of the compound (2*R*,3*S*)-**2l**. Thermal ellipsoids shown at 30% probability.

substrates for the current catalytic systems, and still awaits further effort on the search for more efficient chiral catalysts. Moreover, the asymmetric hydrogenation can be carried out on a relatively large scale. For example, 0.8977 grams of the tetrahydroquinoxaline **2m** was obtained in 89% yield with greater than 99:1 d.r. and 90% ee (Scheme 4).

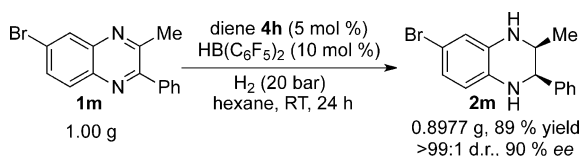
In summary, a metal-free *cis*-selective hydrogenation of a broad range of 2,3-disubstituted quinoxalines using borane catalysts has been successfully realized to furnish 2,3-disubstituted 1,2,3,4-tetrahydroquinoxalines in 80–99% yields with d.r. values of 92:8–> 99:1. Significantly, the highly desirable asymmetric reaction using chiral borane catalysts generated

Table 3: Asymmetric hydrogenation of 2,3-disubstituted quinoxalines.^[a]

Entry	Product (2)	Yield [%] ^[b]	cis/trans ^[c]	ee [%] ^[c]
1		82	> 99:1	89
2		71	> 99:1	77
3		91	> 99:1	96
4 ^[d]		91	98:2	81
5		72	99:1	67
6		87	> 99:1	92
7		85	> 99:1	94
8		85	> 99:1	90
9 ^[d]		75	98:2	96
10 ^[d]		85	98:2	86
11 ^[d]		93	> 99:1	77
12 ^[d]		87	99:1	86
13		89	> 99:1	92
14		99	> 99:1	92

[a] All reactions were carried out with 2,3-disubstituted quinoxaline (0.25 mmol), HB(C₆F₅)₂ (10 mol%), chiral diene **4h** (5 mol%), and H₂ (20 bar), in n-hexane (3.7 mL) at room temperature for 24 h unless other noted. [b] Yield of isolated product. [c] Determined by HPLC using a Chiralcel OD-H column, except for that in entry 12 for which a Chiralpak IC column was used. [d] At 50 °C.

by the in situ hydroboration of the chiral diene **4h** with HB(C₆F₅)₂ under mild reaction conditions has been achieved to furnish optically active products with up to 96% ee. Further



Scheme 4. Asymmetric hydrogenation on a gram scale.

study for efficient catalysts and their application for the metal-free hydrogenation of other unsaturated compounds is underway in our laboratory.

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- [17] CCDC 1026035 (**21**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.