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The First General, Efficient and Highly Enantioselective Reduction of Quinoxalines and Quinoxalinones

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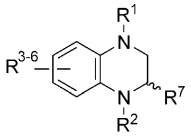
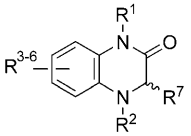
Tetrahydroquinoxalines and dihydroquinoxalinones possess important biological and pharmacological properties.[1] By 1947 various tetrahydroquinoxalines had already been synthesized to examine their antimalarial activity.[2] Since then interest in the tetrahydroquinoxalines and dihydroquinoxalinones has significantly increased.



1,2,3,4-Tetrahydroquinoxaline



3,4-Dihydroquinoxalinone

They function as potent inhibitors of glycoproteins; including DC-SIGN,[3] which facilitates the spread of viruses such as HIV, Hepatitis C, or Ebola; or CETP, which in its inhibited state counteracts atherosclerosis.[4] Furthermore, they have been reported to open calcium channels;[5] or serve as highly selective antagonists for diverse receptors, for example Kinin B_1, which is associated with inflammation and pain in septicemia.[6] An example of a promising dihydroquinoxalinone is GW420867X, a non-nucleoside HIV-1 reverse transcriptase inhibitor, which is currently in clinical trials.[7] Furthermore, due to the similarity in their structure, tetrahydroquinoxalines are used as models for tetrahydrofolic acids (coenzyme F) and their derivatives, for example, leucovorine.[8] The latter serves as a "rescue agent" in chemotherapy together with methotrexate. Even though it is only the natural diastereomer of leucovorine that acts as a competitive inhibitor, and the possibility that long-term use of the unnatural diasteromer may be toxic, leucovorine is still generally used as a racemate due to the lack of alternative synthetic methods. Despite the great importance of the tetahydroquinoxalines and dihydroquinoxalinones there are only very few enantioselective synthetic routes. To date efficient synthetic methods include catalytic reactions[9] or solid-phase synthesis.[10] However, they generally require multiple reaction steps and the introduction of a chiral amino alcohol or a corresponding amino acid.[11] With particular emphasis on economic and ecologically valuable processes, asymmetric hydrogenation represents a highly efficient and atom-economic approach.[12]

General, catalytic, enantioselective hydrogenations of quinoxalines and quinoxalinones are not known, yet they represent the simplest method for synthesizing optically active tetrahydroquinoxalines and dihydroquinoxalinones. To date only the catalytic enantioselective reduction of 2-methylchinoxaline has been described.[13,14] However, for instance in the case of DC-SIGN, as is often the case with tetrahydroquinoxalinones, the ones with aromatic substituents in the 2-position are more biologically active.

Therefore, we decided to examine a general, catalytic, enantioselective reduction of both quinoxalines and quinoxalinones. In particular, we wanted to concentrate on aryl-substituted derivatives, as these have been shown to be especially biologically active. As our initial work towards a metal-catalyzed, asymmetric reduction did not deliver the desired results with regard to high reactivity and selectivity, we decided to also examine metal-free transfer hydrogenations.[15,16] Here, the initial experiments showed that various Brønsted acids such as diphenylphosphate are able to catalyze the transfer hydrogenation of quinoxaline **1a** to the corresponding 2-phenyl-tetrahydroquinoxaline **3a** in the presence of the Hantzsch dihydropyridine **2a** as a hydride source. Further, it was shown that the concentration of the solvent is a determining reaction parameter, especially with regard to the reactivity: The reactivity continuously increases with increasing solvent concentration.

The following studies concentrated on the development of the first asymmetric variant in which the chiral phosphoric

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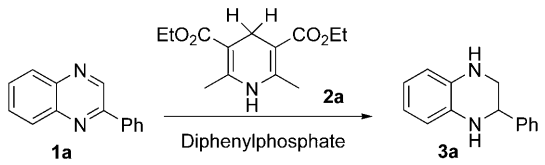
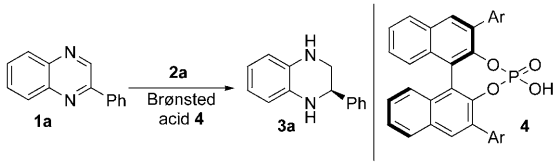


acid diesters **4a–4f** (Table 1) were employed.[17] Here only minimal differences in the reactivity were seen, while the enantioselectivity varied greatly. The best results with

Table 1. Survey of chiral Brønsted acid catalysts for the enantioselective reduction of quinoxalines.



Entry[a]	Catalyst	Ar	Conv. [%][b]	e.r.[c]
1	**4a**	1-naphthyl	98	78:22
2[d]	**4a**	1-naphthyl	98	64:36
3	**4b**	2-naphthyl	97	55:45
4	**4c**	9-phenanthryl	98	82:18
5[d]	**4c**	9-phenanthryl	99	80:20
6	**4d**	Ph_3Si, $[H]_8$	66	−53:47
7	**4e**	anthracenyl	100	95:5
8[e]	**4e**	anthracenyl	100	94:6
9[e]	**4f**	2,4,6-(iPr)$_3$-phenyl	100	94:6

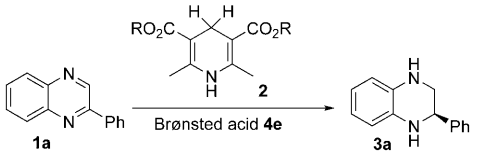
[a] Reaction conditions: **1a**, **2a** (2.4 equiv) and **4** (10 mol%), 40°C, chloroform (0.5 M), 24 h. [b] Conversions were determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [c] Enantiomeric excess was determined by HPLC using Chiralcel OD-H. [d] In toluene (0.5 M) at 60°C. [e] 5 mol% of catalyst was used.

regard to conversion and enantioselectivities were observed with Brønsted acid catalyst **4e** in chloroform, which on full conversion resulted in the formation of 2-phenyl-tetrahydroquinoxalines with an excellent enantiomeric ratio of 95:5 e.r. (Table 1, entry 7). The use of **4f** gave a similar result (Table 1, entry 9), whereas the other phosphoric acid diesters resulted in considerably lower selectivities (Table 1, entries 1–6).

While the steric demand in the 3,3′-position of the BINOL skeleton has a significant impact on the asymmetric induction, the steric demand of the hydride source plays a lesser role. Thus, the best result was achieved with Hantzsch diethyl ester **2a** (Table 2, entry 1), whereas the other Hantzsch esters **2b–2d** showed reduced enantioselectivities (Table 2, entries 2–4).

Additionally, the variation of the temperature had negligible impact on the transfer hydrogenations that we examined. Over a temperature range from room temperature to 50°C, both the reactivities and the enantioselectivities changed only minimally. Thus, we conducted the reductions at 35°C. Using the optimized reaction conditions we tested the substrate scope of this first organocatalytic, enantioselective reduction by employing various 2-aryl- and hetroaryl-

Table 2. Effect of various Hantzsch esters on the transfer hydrogenation of quinoxalines.



Entry[a]	HEH	R	Conv. [%][b]	e.r.[c]
1	**2a**	ethyl	94	95:5
2	**2b**	allyl	85	90:10
3	**2c**	*tert*-butyl	45	92:8
4	**2d**	benzyl	89	92:8

[a] Reaction conditions: **1a**, **2a** (2.4 equiv) and **4e** (5 mol%), 50°C, chloroform (0.5 M), 24 h. [b] Conversions were determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [c] Enantiomeric excess was determined by HPLC using Chiralcel OD-H.

quinoxalines (Table 3). It was thereby shown that diverse 2-aryl-tetrahydroquinoxalines **3a–3n** with electron-withdrawing as well as electron-donating substituents can be isolated in good yields and with excellent enantioselectivities (up to 98% *ee*).[18]

Interestingly, the metal-free hydrogenation is also compatible with various halogenation patterns, enabling easy variations of both, the aryl substituent as well as the tetrahydroquinoxaline core. The absolute configuration of the product was established by means of an X-ray structure analysis of compound **3e** (Figure 1).

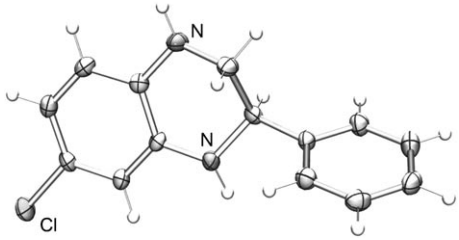
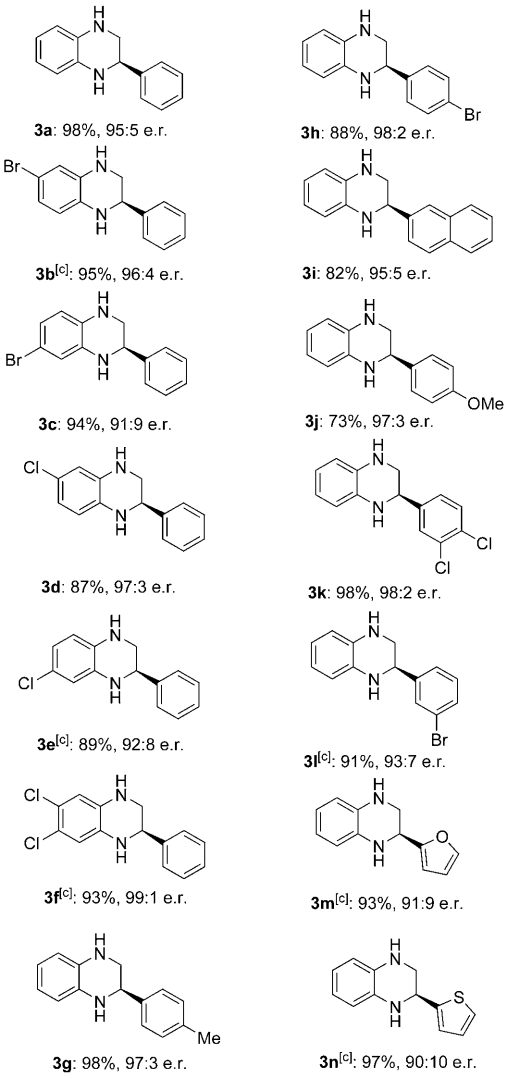


Figure 1. Molecular structure of (*R*)-7-Chloro-2-phenyl-1,2,3,4-tetrahydroquinoxaline **3e**.

During the further course of our studies we decided to extend our transfer hydrogenation procedure to incorporate quinoxalinones, as to date no asymmetric reduction for these important substrates has been developed. To our delight, the reaction proceeds with high enantioselectivities. In contrast to the reduction of the benzopyrazines, in this instance the reactions were carried out in THF at 50°C. This change was necessary due to the lower solubility of the quinoxalinones (Table 4). Thus, for the first time various dihydroquinoxalinones **5a–e** were obtained with excellent enantioselectivities (up to 98% *ee*).

In summary, we have developed the first highly enantioselective reduction of both quinoxalines as well as quinoxalinones. The new method can effectively be applied in the transformation of diverse aryl-substituted quinoxalines and

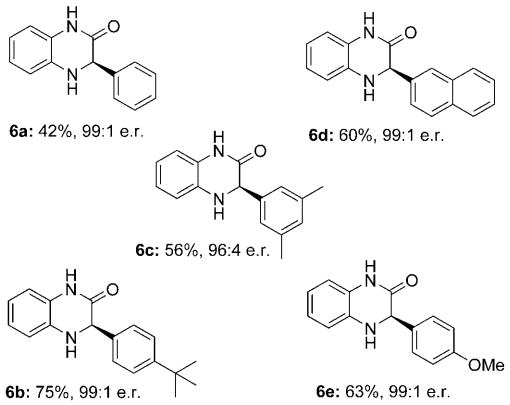
Table 3. Scope of the asymmetric Brønsted acid catalyzed reduction of quinoxalines **1**.



[a] Reaction conditions: **1a**, **2a** (2.4 equiv) and **4** (10 mol%), 35°C, chloroform (0.5 M), 24 h. [b] Isolated yields after column chromatography. Enantiomeric excess was determined by HPLC using Chiralcel OD-H. [c] Reaction was performed using Brønsted acid **4f**.

quinoxalinones into the biologically and pharmacologically relevant 2-tetrahydroquinoxalines and 3-dihydroquinoxalinones with excellent enantioselectivities (up to 98% *ee*). The mild organocatalytic reaction conditions also allow various halogenation patterns, which may be useful for further derivatization. In contrast to existing synthetic routes, the method we have developed is not based on the introduction of chiral residues but rather provides the desired optically active products by a simple, direct, and fast enantioselective reduction step, which will be useful for application in the synthesis of fine chemicals, as well as agro- and pharmaceutical products.

Table 4. Scope of the asymmetric Brønsted acid catalysed reduction of quinoxalinones **5**.



[a] Reaction conditions: **5a**, **2a** (2.4 equiv) and **4** (10 mol%), 50°C, THF (0.2 M), 24 h. [b] Isolated yields after column chromatography. Enantiomeric excess was determined by HPLC using Chiralcel OD-H.

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Keywords: Brønsted acid · Hantzsch ester · organocatalysis · pyrazine · pyridine · transfer hydrogenation

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[18] Applying these reaction conditions to alkyl-substituted quinoxalines resulted so far in lower enantioselectivities. For instance 2-methyltetrahydroquinoxaline can be isolated with an enantiomeric excess of 64% *ee*.

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