

Convergent Asymmetric Disproportionation Reactions: Metal/Brønsted Acid Relay Catalysis for Enantioselective Reduction of Quinoxalines

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Supporting Information

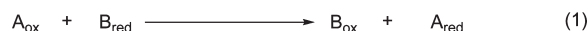
ABSTRACT: A convergent asymmetric disproportionation of dihydroquinoxalines for the synthesis of chiral tetrahydroquinoxalines using a metal/Brønsted acid relay catalysis system has been developed. The use of hydrogen gas as the reductant makes the convergent disproportionation an ideal atom-economical process. A dramatic reversal of enantioselectivity was observed in the reduction of quinoxalines because of the different steric demands in the 1,2- and 1,4-hydride transfer pathways.

Reduction–oxidation (redox) reactions constitute one of the most fundamental reaction types in chemistry. They result in changes in the oxidation numbers of the participating chemical species. Addition of hydrogen or electrons or removal of oxygen is reduction, and removal of hydrogen or electrons or addition of oxygen is oxidation. Both oxidation and reduction occur simultaneously and in equivalent amounts during any reaction involving either process (eq 1 in Scheme 1). A redox reaction is called a disproportionation (or dismutation) reaction when the starting element is both oxidized and reduced (eq 2 in Scheme 1). In general, the atom economy of disproportionation reactions is not very good because the reaction simultaneously gives an oxidation product and a reduction product. If the reduction product is the target compound, the atom economy would be significantly improved if the starting material could be regenerated from the oxidation product with the aid of a reductant. Thus, a convergent disproportionation reaction would be realized: (1) initially, the oxidation product would deliver the starting material in the presence of the reductant; (2) subsequently, the starting material would undergo the disproportionation reaction to give the desired reduction product and regenerate the oxidation product for next redox cycle (eq 3 in Scheme 1). H_2 is a preferred reductant for the generation of starting materials because it is the cheapest reducing agent and yields no requisite byproducts.² Herein we report metal/Brønsted acid relay catalysis for the asymmetric hydrogenation of quinoxalines through a convergent disproportionation of dihydroquinoxalines (eq 4 in Scheme 1).^{3–5} A dramatic reversal of enantioselectivity was also observed for hydrogenation relative to transfer hydrogenation of quinoxalines promoted by chiral phosphoric acid.⁶

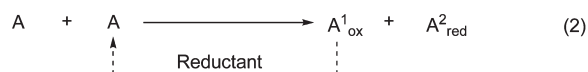
In our studies of asymmetric hydrogenation and transfer hydrogenation of heteroaromatic compounds,^{7–9} a serendipitous disproportionation of dihydroquinoxaline **4a** was observed. In spite of its sensitivity to air, dihydroquinoxaline **4a** showed a greater tendency to undergo the unexpected self-transfer hydrogenation at room temperature (rt) (eq 5 in Scheme 2). To our delight, the self-transfer hydrogenation of **4a** delivered **3a** with excellent 93% ee in the presence of chiral phosphoric acid (S)-**1b** (eq 6 in Scheme 2).

Scheme 1. Convergent Asymmetric Disproportionation

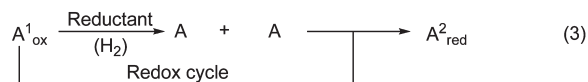
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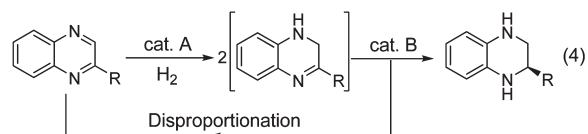
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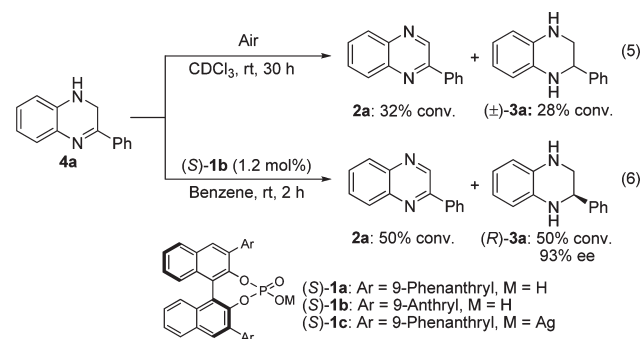
Convergent Disproportionation Reaction:



This work: Convergent Asymmetric Disproportionation



Scheme 2. Self-Transfer Hydrogenation of Dihydroquinoxaline

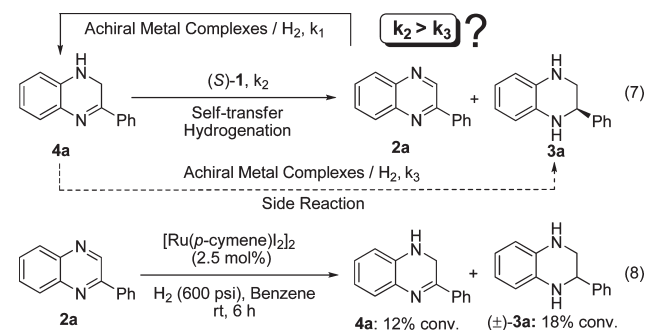


Recently, Xiao^{10a–c} and Rueping^{10d} developed highly enantioselective hydrogenations of acyclic imines and quinolines employing combined Brønsted acid and chiral diamine-ligated Ir(III) catalysts. Rueping and co-workers reported a highly enantioselective Brønsted acid-catalyzed transfer hydrogenation of quinoxalines with Hantzsch esters (HEH).^{8i,11} Inspired by Xiao and Rueping's work, we envisaged that hydrogen gas activated by achiral metal complexes could reduce

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Scheme 3. Hydrogenation of Quinoxalines



2a to dihydroquinoxaline **4a**, ultimately affording chiral **3a** with complete conversion through convergent asymmetric disproportionation of **4a** in the presence of chiral phosphoric acid **1** (eq 7 in Scheme 3). The key point to warrant our above hypothesis is the difference between the reaction rates for self-transfer hydrogenation of **4a** (k_2) promoted by chiral phosphoric acid and the background hydrogenation of **4a** (k_3) catalyzed by metal complexes that generate **3a** in racemic form (eq 7 in Scheme 3). From a survey of achiral metal precursors, $[\text{Ru}(p\text{-cymene})\text{I}_2]_2$ emerged as a suitable catalyst for in situ generation of dihydroquinoxaline **4a** because of its low efficiency in giving **3a** (eq 8 in Scheme 3).

Initially, moderate conversion (67%) and ee (58%) were obtained in CHCl_3 under 600 psi hydrogen at ambient temperature using $[\text{Ru}(p\text{-cymene})\text{I}_2]_2/(S)\text{-1a}$ as the catalyst (Table 1, entry 1). Further investigations of the solvent effect suggested that benzene was the best solvent for the hydrogenation of 2-phenylquinoxaline with respect to enantioselectivity (80% ee; entries 2–6). Reducing the pressure of hydrogen slightly improved the enantioselectivity (81% ee) but deteriorated the catalytic activity (entry 7). A small decrease in ee was observed with increasing reaction temperature (entry 8). The evaluation of chiral phosphoric acids showed that $(S)\text{-1b}$ was the best acid for this transformation in terms of enantioselectivity (90% ee; entry 9). Tetrahydroquinoxaline **3a** was not observed upon the addition of silver phosphate/ $(S)\text{-1c}$, which undergoes an exchange of counterion with Ru(II) complex; thus, a chiral-counterion-oriented ruthenium-catalyzed asymmetric hydrogenation process was excluded (entry 10). Complete conversion was obtained by prolonging the reaction time, albeit with a slight decrease in ee (entry 11). Interestingly, the best results with respect to reactivity and enantioselectivity were achieved when the catalyst loading was reduced to 1 mol % (entry 13). Notably, 91% conversion was obtained at substrate-to-catalyst ratios of 1000 that the catalyst loading was relatively low in the asymmetric transformation involving chiral phosphoric acids (entry 15). Therefore, the optimal conditions were established to be $[\text{Ru}(p\text{-cymene})\text{I}_2]_2$ (0.5 mol %)/ $(S)\text{-1b}$ (1.2 mol %)/ H_2 (600 psi)/benzene/rt.

With the optimized conditions in hand, we explored the scope of the enantioselective synthesis of tetrahydroquinoxalines through convergent disproportionation of dihydroquinoxalines (Table 2). In general, excellent yields and enantioselectivities were obtained in the asymmetric reduction of various quinoxalines promoted by self-transfer hydrogenation of dihydroquinoxalines (entries 1, 3, 5–7, and 9–13). A moderate yield (51%) but excellent enantioselectivity (93%) were obtained in the hydrogenation of 6-chloro-2-phenylquinoxaline (entry 15). Interestingly, an unexpected reversal of enantioselectivity for the convergent disproportionation of dihydroquinoxalines promoted by H_2 relative to the pure organocatalytic transfer hydrogenation of quinoxalines with Hantzsch esters developed by

Table 1. Metal/Bronsted Acid-Catalyzed Asymmetric Reduction of 2-Phenylquinoxaline^a

entry	solvent	1	X	conv. (%) ^b	ee (%) ^c
1	CHCl_3	$(S)\text{-1a}$	2.5	67	58
2	CH_2Cl_2	$(S)\text{-1a}$	2.5	95	45
3	MeOH	$(S)\text{-1a}$	2.5	>95	2
4	THF	$(S)\text{-1a}$	2.5	>95	10
5	toluene	$(S)\text{-1a}$	2.5	85	79
6	benzene	$(S)\text{-1a}$	2.5	87	80
7 ^d	benzene	$(S)\text{-1a}$	2.5	28	81
8 ^e	benzene	$(S)\text{-1a}$	2.5	>95	77
9	benzene	$(S)\text{-1b}$	2.5	78	90
10 ^f	benzene	$(S)\text{-1c}$	2.5	—	—
11 ^g	benzene	$(S)\text{-1b}$	2.5	>95	86
12 ^g	benzene	$(S)\text{-1b}$	1.25	>95	88
13 ^g	benzene	$(S)\text{-1b}$	0.5	>95	90 (R)
14 ^g	benzene	$(S)\text{-1b}$	0.25	>95	89
15 ^g	benzene	$(S)\text{-1b}$	0.05	91	84

^a Conditions: **2a** (0.05 mmol), $[\text{Ru}(p\text{-cymene})\text{I}_2]_2$ (2.5 mol %), $(S)\text{-1}$ (6 mol %), H_2 (600 psi), solvent (2 mL), 16 h, rt. ^b Determined by ^1H NMR analysis. ^c Determined by HPLC. ^d H_2 (400 psi). ^e 40 °C. ^f $(S)\text{-1c}$ (11 mol %). ^g **2a** (2.0 mmol), 48 h.

Table 2. Asymmetric Reduction of Quinoxalines through Convergent Disproportionation of Dihydroquinoxalines^a

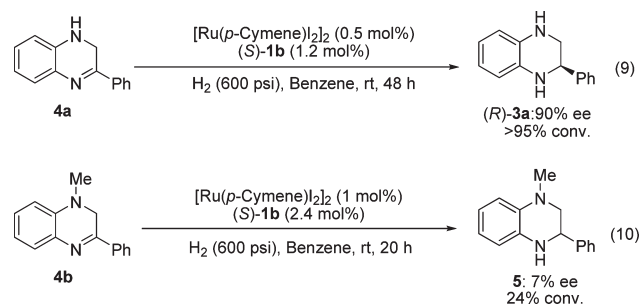
entry	Ar in 2	R in 2	yield (%) ^b	ee (%) ^c
1	Ph	H	96 (3a)	90 (R)
2 ^d	Ph	H	98 (3a)	90 (S)
3	4-MeC ₆ H ₄	H	98 (3b)	83 (R)
4 ^d	4-MeC ₆ H ₄	H	98 (3b)	94 (S)
5	4-FC ₆ H ₄	H	98 (3c)	89 (R)
6	4-ClC ₆ H ₄	H	98 (3d)	87 (R)
7	4-BrC ₆ H ₄	H	97 (3e)	87 (R)
8 ^d	4-BrC ₆ H ₄	H	88 (3e)	96 (S)
9	4-CF ₃ C ₆ H ₄	H	95 (3f)	86 (R)
10	3-FC ₆ H ₄	H	98 (3g)	90 (R)
11	3-ClC ₆ H ₄	H	96 (3h)	93 (R)
12	3-BrC ₆ H ₄	H	97 (3i)	94 (R)
13	2-naphthyl	H	98 (3j)	94 (R)
14 ^d	2-naphthyl	H	82 (3j)	90 (S)
15	Ph	6-Cl	51 (3k)	93 (R)

^a Conditions: **2** (0.20 mmol), $[\text{Ru}(p\text{-cymene})\text{I}_2]_2$ (0.5 mol %), $(S)\text{-1b}$ (1.2 mol %), H_2 (600 psi), benzene (2 mL), 48 h, rt. ^b Isolated yields. ^c Determined by HPLC. ^d Data quoted from ref 8i. $(R)\text{-1b}$ was used in Rueping's work for the formation of $(R)\text{-3a}$. For a simple discussion, $(S)\text{-1b}$ was employed in this table. Reaction conditions: **2** (0.1 mmol), Hantzsch ethyl ester (0.24 mmol), $(S)\text{-1b}$ (10 mol %), 35 °C, CHCl_3 (0.5 M), 24 h.

Rueping and co-workers (entries 1 vs 2, 3 vs 4, 7 vs 8, and 13 vs 14) was observed.⁸ⁱ 2-Alkyl-substituted quinoxalines were also tested but resulted in low enantioselectivities because of enhancement of the background reaction.

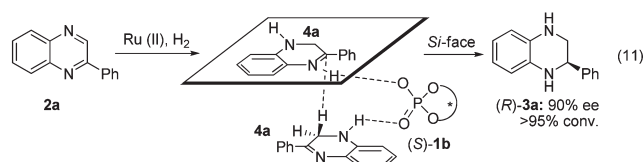
Further experiments were focused on elucidation of the role played by the N-H in intermediate **4a** in regard to enantioselective control in the convergent disproportionation process (Scheme 4). As predicted,

Scheme 4. Hydrogenation of Dihydroquinoxalines 4a and 4b

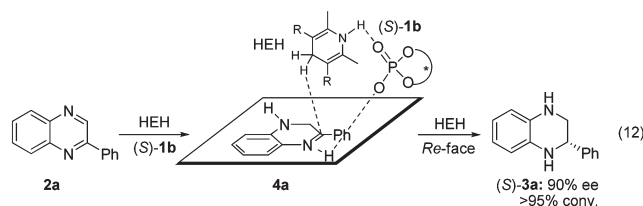


Scheme 5. Origin of Enantioversional in the Asymmetric Reduction of Quinoxalines Resulting from Different Hydride Transfer Paths

This Work: Self-transfer hydrogenation (1,2 H-transfer)



Rueping's work: HEH-transfer hydrogenation (1,4 H-transfer)



the hydrogenation of intermediate 4a gave tetrahydroquinoxaline 3a with the same enantioselectivity as in the hydrogenation of 2a (eq 9 in Scheme 4). Poor ee (7%) and low conversion (24%) were observed in the hydrogenation of N-methyl-3,4-dihydroquinoxaline 4b because of its inability to undergo self-transfer hydrogenation (eq 10 in Scheme 4).¹² These results suggest that the N-H in intermediate 4a is crucial for the realization of convergent disproportionation.

The origin of enantioversional in the asymmetric reduction of quinoxalines can be explained by the stereochemical model illustrated in Scheme 5. For convergent disproportionation of dihydroquinoxalines, the hydrogenation of 2a first delivers intermediate 3,4-dihydroquinoxaline 4a, which subsequently interacts with chiral phosphoric acid (S)-1b through two hydrogen bonds (eq 11 in Scheme 5). These two hydrogen bonds with the phosphate and the effect of steric hindrance build up a "three-point contact model" that determines the stereoselectivity in the disproportionation of 3,4-dihydroquinoxaline 4a. In the pure organocatalytic process, 4a/(S)-1b/HEH form another "three-point contact model" leading to Re-face reduction on the basis of Goodman and Himo's calculation (eq 12 in Scheme 5).¹³ The reversal of enantioselectivity perhaps lies in the different steric demands of the 1,2-hydride transfer pathway in the self-transfer hydrogenation of 4a and the 1,4-hydride transfer pathway using HEH (Scheme 5).

Density functional theory calculations at the B3LYP/6-31G** level were carried out to validate this proposal (Figure 1). The transition state TS-R for the formation of (R)-3a is more favorable than TS-S by 1.01 kcal/mol, in good agreement with the experimental observations.

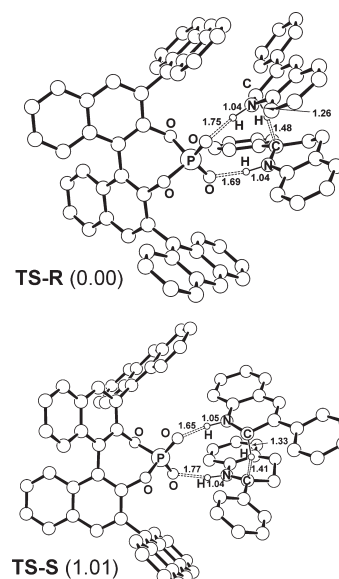
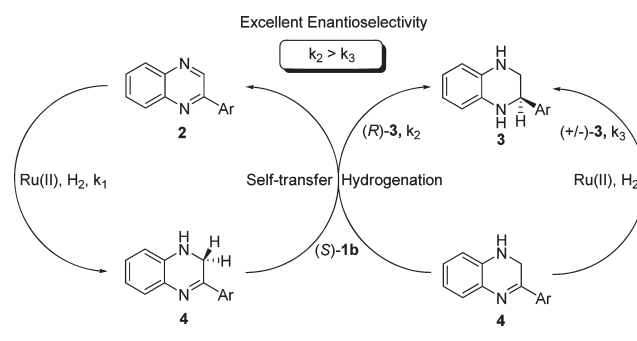


Figure 1. Transition states for the self-transfer hydrogenation. Bond lengths are given in Å, and relative electronic energies in kcal/mol are given in parentheses. Hydrogen atoms, except those forming hydrogen bonds, have been omitted for clarity.

Scheme 6. Proposed Mechanism for the Convergent Asymmetric Disproportionation of Dihydroquinoxalines



The theoretical studies provided additional evidence to support the self-transfer hydrogenation mechanism proposed in Scheme 5.

Concerning the mechanism, we assume that the hydrogenation of quinoxalines 2 first generates dihydroquinoxalines 4 with ruthenium(II) as the catalyst (Scheme 6). Subsequently, the intermediates 4 undergo self-transfer hydrogenation to deliver primary starting materials 2 and final products 3 in the presence of Brønsted acid (S)-1b. The detection of intermediate 4a in the hydrogenation of 2a without the addition of Brønsted acid (S)-1b suggests that the first hydrogenation process catalyzed by ruthenium(II) is the rate-determining step (eq 8 in Scheme 3). Therefore, the excellent enantioselectivities observed in this transformation are attributed to the fact that the reaction rate of this principal reaction (k_2) is higher than that of the undesired side reaction (k_3) (Scheme 6).

In summary, we have successfully developed an efficient metal/Brønsted acid relay catalysis system for the highly enantioselective hydrogenation of quinoxalines through convergent asymmetric disproportionation of dihydroquinoxalines with up to 94% ee. Employing hydrogen gas as the reductant makes this convergent disproportionation an ideal atom-economical process. A dramatic reversal of enantioselectivity was observed for the hydrogenation relative to the

transfer hydrogenation of quinoxalines promoted by chiral phosphoric acids because of the different steric demands for the 1,2- and 1,4-hydride transfer pathways. Asymmetric transfer reduction of benzoxazines was also realized using catalytic amounts of quinoxalines under hydrogenation conditions.¹⁴ Further study will be directed toward the extension of this strategy to other synthetically interesting compounds.

■ ASSOCIATED CONTENT

S Supporting Information. Complete experimental procedures and characterization data for the prepared compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (12) Low conversion (30%) and almost 0% ee were obtained when 3-phenyl-2H-1,4-benzoxazine replaced **4b** as the starting material in eq 10 in Scheme 4. When compounds **4a** and **4b** (1:1) were reacted in the same reaction vessel in benzene, the ee of **3a** was 93% and compound **5** was obtained in 94% ee as a result of the hydride transfer from **4a** to **4b** in the presence of chiral phosphoric acid (**S**)-**1b**. A mixture of **5** and **3a** (1.00:0.64) suggested that the formation of **3a** was not faster than that of **5**.
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