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Asymmetric Hydrogenation of 2- and 2,3-Substituted Quinoxalines with Chiral Cationic Ruthenium Diamine Catalysts

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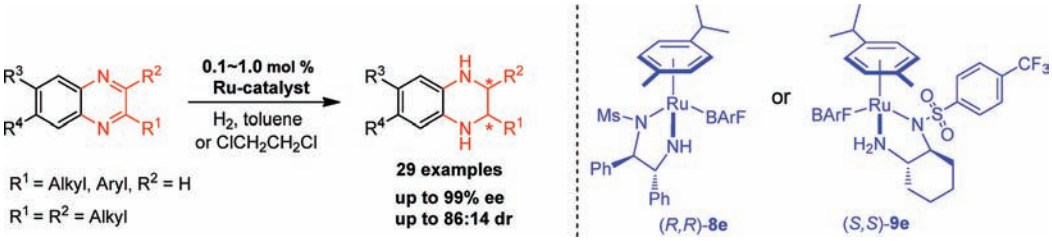
ABSTRACT



The enantioselective hydrogenation of 2-alkyl- and 2-aryl-subsituted quinoxalines and 2,3-disubstituted quinoxalines was developed by using the cationic Ru(η^6-cymene)(monosulfonylated diamine)(BArF) system in high yields with up to 99% ee. The counteranion was found to be critically important for the high enantioselectivity and/or diastereoselectivity.

The 1,2,3,4-tetrahydroquinoxaline ring system is a useful key structural unit in many therapeutically and biologically active compounds.[1] Optically pure tetrahydroquinoxalines have shown great potential for drug development.[1c−h] Consequently, increasing research efforts have been devoted to the asymmetric synthesis of these compounds over the past decades.[2−5] Among the reported different methods, asymmetric hydrogenation (AH) of the corresponding readily available quinoxalines represents one of the most convenient and straightforward approaches for attaining such optically active heterocyclic compounds.

In recent years, great progress in the metal-catalyzed AH of heteroaromatic compounds,[6] particularly quinolines,[7] has been made. However, despite the great importance of tetahydroquinoxalines, few successful examples of AH of quinoxalines have been reported so far in the literature.[5] The first AH of 2-methyl-quinoxaline with a Rh-DIOP catalyst was reported by Murata in 1987, however with

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only 3% ee.[5a] Since then, much effort has been made by several research groups to expand the substrate scope and to improve the reactivity and enantioselectivity of such a transformation. Most recently, Chan and Fan reported an efficient Ir/H_8-binapo system for AH of 2-alkyl-substituted quinoxalines with high enantioselectivities (up to 96% ee) at low catalyst loading.[5g] Simultaneously, Feringa and coworkers realized the enantioselective hydrogenation of a range of 2-substituted quinoxalines with an iridium catalyst containing monodentate phosphoramidite PipPhos ligand by using piperidine hydrochloride as an additive with up to 96% ee.[5h] Later Ratovelomanana-Vidal and coworkers described an iridium-difluorphos catalyzed AH of 2-alkyl and 2-aryl-substituted quinoxalines with up to 95% ee.[5k] However, all these metallic catalysts had at least one phosphine ligand around the metal center and were often air sensitive. Furthermore, most of these catalysts were highly enantioselective only in the hydrogenation of 2-alkyl-substituted quinoxalines. To the best of our knowledge, AH of 2,3-disubstituted quinoxalines has not been reported so far. Therefore, more general, efficient, and stable catalyst systems for AH of quinoxaline derivatives are desirable.

Recently, we have found that the cationic ruthenium complexes of chiral monotosylated diamines were very efficient catalysts for AH[8] of a broad range of quinoline derivatives, providing chiral 1,2,3,4-tetrahydroquinolines with up to 99% ee.[9] Further mechanistic study indicated that the counteranion is critically important for the high enantioselectivity,[9b] which may provide a suitable platform for extending the application of this Ru-diamine catalyst in the AH of other difficult substrates. Most recently, this catalytic system has been demonstrated to be highly enantioselective for AH of the often-problematic acyclic and cyclic *N*-alkyl imines with up to 99% ee.[10] It was found that the weakly coordinating counterions did influence the enantioselectivity significantly. Encouraged by these results and as our continuing interest in the AH of heteroaromatic compounds and imines, herein, we report the general and highly efficient asymmetric hydrogenation of a broad range of 2-alkyl- and 2-aryl-substituted and 2,3-dialkyl-substituted quinoxalines using a ruthenium-diamine catalytic system to give 1,2,3,4-tetrahydroquinoxaline derivatives in excellent enantioselectivities.

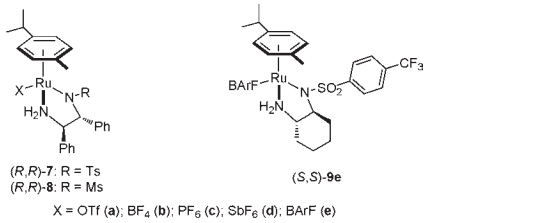

Figure 1. Screened catalysts.

The study was initiated by screening the Ru catalysts containing different chiral diamine ligands and counteranions using 2-methylquinoxaline (**1a**) as the standard substrate (Figure 1). According to our previous reports on the AH of quinolines,[9] we examined the AH of **1a** catalyzed by (*R*,*R*)-**7a** (1 mol %) in methanol (entry 1 in Table 1). The reaction proceeded smoothly, affording (*R*)-2-methyl-1,2,3,4-tetrahydroquinoxaline in quantitative yield, but with only 23% ee. Gratifyingly, a distinct increase in enantioselectivity was observed when aprotic dichloromethane (DCM) was used as solvent (entry 2). Further investigation of a variety of catalysts demonstrated that the counteranion of the catalyst had a significant impact on the stereochemical outcome of the reaction (entries 3−7 and Table S1 in Supporting Information (SI)). A full conversion and excellent enantiomeric excess of 98% were obtained with the weakly coordinating counterion $BArF^-$ (tetrakis(3,5-bis-trifluoromethylphenyl)borate) (entry 7). In addition, for the AH of **1a** with 1.0 mol % (*R*,*R*)-**8e**, DCM, toluene, or $ClCH_2CH_2Cl$ (DCE) all gave excellent enantioselectivities, while DCE resulted in the highest reactivity (entries 7−9). It was also observed that the enantioselectivity is insensitive to hydrogen pressure and temperature (entries 9−13). Furthermore, lowering

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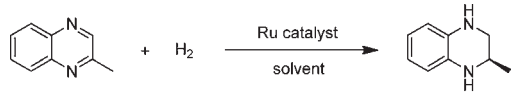
the catalyst loading to 0.1 mol % led to a remarkable decrease in both reactivity and enantioselectivity (entry 14), whereas increasing the substrate concentration (from 0.1 to 1.0 mol/L; 2.0 g scale) could maintain the same enantioselectivity (entry 15). Remarkably, full conversion was also observed when the hydrogenation was carried out at a substrate/catalyst ratio of 1000 under solvent-free conditions, with a slightly lower enantioselectivity (entry 16).

Table 1. Optimization of Reaction Conditions[a]



1a 2a

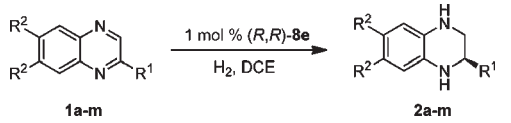
entry	catalyst	solvent	H_2 (atm); temp (°C)	conv (%)[b]	ee (%)[c]
1	(*R*,*R*)-**7a**	MeOH	50; 40	>99	23
2	(*R*,*R*)-**7a**	DCM	50; 40	>99	75
3	(*R*,*R*)-**8a**	DCM	50; 40	>99	69
4	(*R*,*R*)-**8b**	DCM	50; 40	>99	87
5	(*R*,*R*)-**8c**	DCM	50; 40	>99	90
6	(*R*,*R*)-**8d**	DCM	50; 40	>99	91
7	(*R*,*R*)-**8e**	DCM	50; 40	>99 (42)[d]	98
8	(*R*,*R*)-**8e**	toluene	50; 40	>99 (40)[d]	98
9	**(*R*,*R*)-8e**	**DCE**	**50; 40**	**>99 (75)[d]**	**98**
10	(*R*,*R*)-**8e**	DCE	80; 40	>99	98
11	(*R*,*R*)-**8e**	DCE	10; 40	92	98
12	(*R*,*R*)-**8e**	DCE	50; 60	>99	98
13	(*R*,*R*)-**8e**	DCE	50; 20	>99	98
14[e]	(*R*,*R*)-**8e**	DCE	50; 40	38	59
15[f]	(*R*,*R*)-**8e**	DCE	50; 40	95[g]	98
16[h]	(*R*,*R*)-**8e**	solvent-free	50; 40	>99	93

[a] Reaction conditions: 0.2 mmol of **1a** with 1.0 mol % Ru-catalyst in 2 mL of solvent, 12 h. [b] Determined by ^{1}H NMR of the crude reaction mixture. [c] Determined by chiral HPLC. [d] Value in parentheses was related to reaction time of 1.5 h. [e] With 0.1 mol % catalyst, 0.5 mmol of **1a** in 5 mL of DCE, 24 h. [f] With 0.1 mol % catalyst, 14 mmol (2.0 g) of **1a** in 14 mL of DCE, 24 h. [g] Isolated yield. [h] 114 mg of **1a** (1 mmol) with 0.1 mol % catalyst under solvent-free conditions for 24 h.

Under the optimized reaction conditions (entry 9 in Table 1), a variety of 2-alkyl-substituted quinoxalines were efficiently hydrogenated in the presence of 1.0 mol % (*R*,*R*)-**8e** to afford the corresponding chiral tetrahydroquinoxalines with excellent enantioselectivities (95−99% ee, Table 2). It was found that the presence of a sterically demanding alkyl group, such as *tert*-butyl and cyclohexyl, at the 2-position led to slightly lower enantioselectivities (entries 6 and 8). The presence of substituents at the 6- and 7-positions of the quinoxaline framework had no effect on the enantioselectivity (entries 9−12). In the case of 2-styryl quinoxaline, both the heteroaromatic ring and C=C double bond of styryl were hydrogenated, producing 2-phenethyltetrahydroquinoxaline with high enantiomeric excess (entry 13).

Encouraged by these promising results, we then moved to examine the catalytic efficiency of Ru/diamine-type catalysts in the AH of the more challenging 2-aryl substituted quinoxalines.[3,4,5k] 2-Phenylquinoxaline (**3a**) was used as the model substrate for catalyst screening and

Table 2. AH of 2-Alkyl-Substituted Quinoxalines[a]



1a-m 2a-m

entry	R^1/ R^2 (substrate)	yield (%)[b]	ee (%)[c]
1	Me/H (**1a**)	95	98 (*R*)
2	Et/H (**1b**)	90	99 (*R*)
3	*n*-Pr/H (**1c**)	98	98 (*R*)
4	*n*-Bu/H (**1d**)	92	99 (*R*)
5	*i*-Bu/H (**1e**)	97	98 (*R*)
6	*t*-Bu/H (**1f**)	96	95 (*R*)
7	*n*-Hex/H (**1g**)	95	99 (*R*)
8	*c*-Hex/H (**1h**)	95	97 (*R*)
9	Me/Me (**1i**)	94	99 (*R*)
10	Et /Me (**1j**)	93	99 (*R*)
11	*n*-Pr/Me (**1k**)	95	99 (*R*)
12	*n*-Bu/Me (**1l**)	92	98 (*R*)
13	Styryl/H (**1m**)[d]	90	98 (*R*)

[a] Reaction conditions: 0.2 mmol of substrate (**1a**−**1m**) with 1.0 mol % (*R*,*R*)-**8e** in 1 mL of DCE, 50 atm of H_2, stirred at 40 °C for 8 h. [b] Isolated yield. [c] Determined by chiral HPLC. [d] The conjugated C=C bond was also hydrogenated.

optimization of the reaction conditions. To our delight, hydrogenation of **3a** with 1.0 mol % (*R*,*R*)-**8e** gave very good enantioselectivity (Table 3, entry 1). After a survey of a variety of catalysts (Table S2 in SI), complex (*S*,*S*)-**9e** was found to be the optimal catalyst (entry 2). Further improvement in enantioselectivity was achieved when the reaction was carried out under ascending hydrogen pressure and decreasing reaction temperature (entries 3−7). Under the optimized reaction conditions (entry 7 in Table 3), a variety of 2-aryl-substituted quinoxalines were enantiomerically hydrogenated to afford the corresponding products in good to excellent enantioselectivities (89−96% ee, entries 7−13). It was found that the electronic properties of the substituents at the phenyl ring had no apparent effect on activity and enantioselectivity. However, substrate **3g** with the substituent at the *ortho* position of the phenyl ring gave low enantioselectivity (entry 13). Notably, hydrogenation of **3c** afforded the corresponding product with 96% ee (entry 9), which is, to the best of our knowledge, the highest ee value reported so far for the AH of 2-aryl-substituted quinoxaline derivatives.

Finally, we expanded the substrate scope to the readily accessible 2,3-dialkyl-substituted quinoxalines, and the results were summarized in Table 4. Hydrogenation of **5a** was performed in DCE with 1.0 mol % (*R*,*R*)-**8e**, which was the optimal catalyst for the AH of 2-alkyl-substituted quinoxalines, giving the corresponding product with good diastereoselectivity and excellent enantioselectivity (entry 1). To the best of our knowledge, this is the first time the AH of 2,3-disubstituted quinoxalines was realized.[11] Again, catalyst screening demonstrated that

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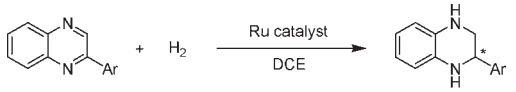
Table 3. AH of 2-Aryl-Substituted Quinoxalines[a]



entry	Ar (substrate)	H_2 (atm)/ temp (°C)	conv (%)[b]	ee (%)[c]
1	C_6H_5 (**3a**)	50/40	>99	84 (*R*)
2	C_6H_5 (**3a**)	50/40	>99	91 (*S*)
3	C_6H_5 (**3a**)	10/40	>99	88 (*S*)
4	C_6H_5 (**3a**)	80/40	>99	92 (*S*)
5	C_6H_5 (**3a**)	50/60	>99	92 (*S*)
6	C_6H_5 (**3a**)	50/20	>99	89 (*S*)
7	**C_6H_5 (3a)**	**80/20**	**90**[d]	**94** (*S*)
8	4-F-C_6H_4 (**3b**)	80/20	92[d]	94 (*S*)
9	4-Cl-C_6H_4 (**3c**)	80/20	94[d]	96 (*S*)
10	4-Br-C_6H_4 (**3d**)	80/20	95[d]	95 (*S*)
11	4-MeO-C_6H_4 (**3e**)	80/20	90[d]	94 (*S*)
12	3-MeO-C_6H_4 (**3f**)	80/20	95[d]	94 (*S*)
13	2-MeO-C_6H_4 (**3g**)	80/20	91[d]	89 (*S*)

[a] Reaction conditions: 0.2 mmol of substrate (**3a**−**3g**) with 1.0 mol % (*S*,*S*)-**9e** (except for entry 1, (*R*,*R*)-**8e**) in 1 mL of DCE, 16 h. [b] Determined by ^{1}H NMR of the crude reaction mixture. [c] Determined by chiral HPLC. [d] Isolated yield.

the counteranion also played an important role in the diastereoselectivity control of this reaction (entries 1−5). After optimization of the reaction conditions (Table S3 in SI), a variety of 2,3-dialkyl substituted quinoxalines were reduced at 40 °C for 8 h in toluene under 50 atm of hydrogen using 1.0 mol % (*R*,*R*)-**8e**. Generally, excellent enantioselectivities (99% ee in all cases) and moderate diastereoselectivities (69/31−86/14) were achieved. It was found that the electronic properties of the substituents at the 6-position of the quinoxaline framework had an apparent effect on diastereoselectivity. Substrates bearing F (**5g**) or Cl (**5h**) gave low diastereoselectivities (entries 12 and 13).

In summary, the half-sandwich Ru(II) complexes of monosulfonylated diamine bearing a weakly coordinating bulky counterion $BArF^-$ have been disclosed to be highly efficient for AH of a variety of 2- and 2,3-substituted quinoxalines, providing a convenient access to the corresponding optically active 1,2,3,4-tetrahydroquinoxalines with biological importance. The counterion was found to be critically important for the high enantioselectivity and/or diastereoselectivity, which may provide a suitable platform for extending their application in the AH of other heteroaromatic compounds. Investigation for detailed insight into the nature of this remarkable counteranion effect is in progress.

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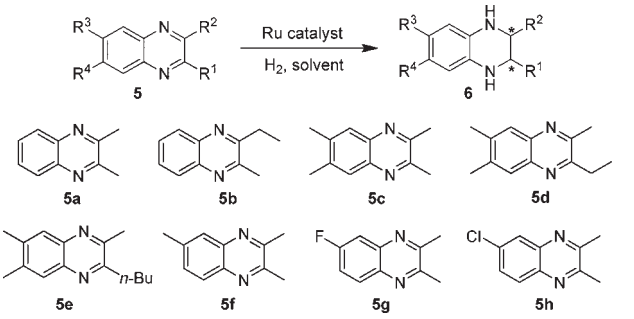
Table 4. AH of 2,3-Dialkyl-Substituted Quinoxalines[a]



entry	catalyst	substrate	solvent	conv (%)[b]	*trans*/*cis*[c]	ee (%)[d]
1	(*R*,*R*)-**8e**	**5a**	DCE	>99	72/28	99 (+)
2	(*R*,*R*)-**8a**	**5a**	DCE	>99	16/84	98 (+)
3	(*R*,*R*)-**8b**	**5a**	DCE	>99	22/78	97 (+)
4	(*R*,*R*)-**8c**	**5a**	DCE	>99	42/58	99 (+)
5	(*R*,*R*)-**8d**	**5a**	DCE	>99	51/49	99 (+)
6	(*R*,*R*)-**8e**	**5a**	toluene	92[e]	80/20	99 (+)
7	(*R*,*R*)-**8e**	**5b**	toluene	94[e]	80/20	99 (+)
8	(*R*,*R*)-**8e**	**5c**	toluene	96[e]	85/15	99 (+)
9	(*R*,*R*)-**8e**	**5d**	toluene	95[e]	86/14	99 (+)
10	(*R*,*R*)-**8e**	**5e**	toluene	94[e]	84/16	99 (+)
11	(*R*,*R*)-**8e**	**5f**	toluene	90[e]	83/17	99 (+)
12	(*R*,*R*)-**8e**	**5g**	toluene	92[e]	69/31	99 (+)
13	(*R*,*R*)-**8e**	**5h**	toluene	91[e]	73/27	99 (+)

[a] Reaction conditions: 0.2 mmol of substrate (**5a**−**h**) with 1.0 mol % Ru-catalyst in 1 mL of solvent, 50 atm of H_2, stirred at 40 °C for 8 h. [b] Determined by ^{1}H NMR of the crude reaction mixture. [c] Determined by ^{1}H NMR[12] and/or HPLC. [d] Determined by chiral HPLC. [e] Isolated yield.

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Supporting Information Available. Experimental procedures, characterization data for all compounds, descriptions of stereochemical assignments, and copies of ^{1}H and ^{13}C NMR spectra for new compounds reported in the text. This material is available free of charge via the Internet at http://pubs.acs.org.