DOI: 10.1002/adsc.201300604

Asymmetric Hydrogenation of Quinoxalines, Benzoxazines, and a Benzothiazine Catalyzed by Chiral Ruthenabicyclic Complexes

Noriyoshi Arai,[a] Yu Saruwatari,[a] Kotaro Isobe,[a] and Takeshi Ohkuma[a,*]

[a] Division of Chemical Process Engineering and Frontier Chemistry Center, Faculty of Engineering, Hokkaido University, Sapporo, Hokkaido 060-8628, Japan
Fax: (+81)-11-706-6598; e-mail: ohkuma@eng.hokudai.ac.jp

Received: July 8, 2013; Published online: ■■ ■■, 0000

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201300604.

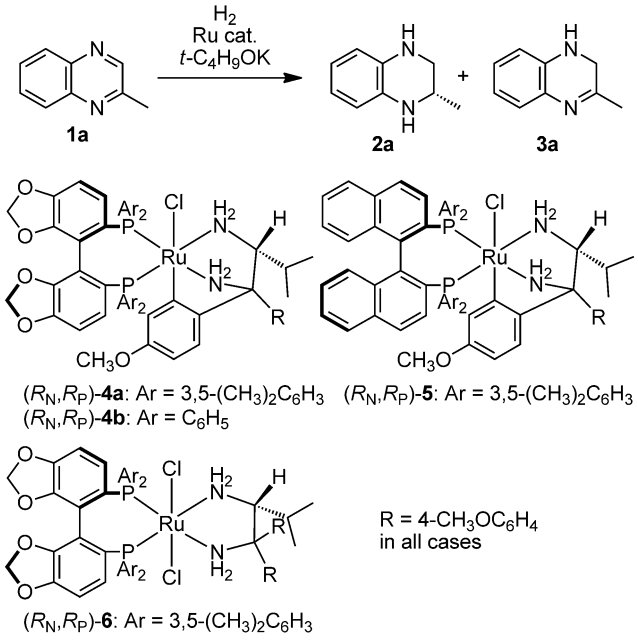
Abstract: The ruthenabicyclic complex RuCl[(*R*)-daipena][(*R*)-dm-segphos] with potassium *tert*-butoxide catalyzes the hydrogenation of 2-alkylquinoxalines and a 3-methyl-2*H*-1,4-benzoxazine in toluene under 20–100 atm of hydrogen at 40 °C to afford *S*-configured cyclic amino products in greater than 97% enantiomeric excess {DAIPENA = anion of DAIPEN at the 2-position of an anisyl group, DAIPEN = 1,1-di(4-anisyl)-2-isopropyl-1,2-ethylenediamine, DM-SEGPHOS = (4,4′-bi-1,3-benzodioxole)-5,5′-diylbis[di(3,5-xylyl)phosphine]}. The high catalytic activity results in a turnover number as high as 9400. Hydrogenation of the benzoimine heterocycles with the RuCl[(*R*)-daipena][(*R*)-segphos]/potassium *tert*-butoxide system yields the *R*-configured products in high enantiomeric excess [SEGPHOS=(4,4′-bi-1,3-benzodioxole)-5,5′-diylbis-(diphenylphosphine)]. The mode of enantioselection is discussed based on transition state models involving six-membered pericyclic structures.

Keywords: amines; asymmetric catalysis; hydrogenation; imines; ruthenium

Optically active 2-substituted 1,2,3,4-tetrahydroquinoxalines as well as 3-substituted 3,4-dihydro-2*H*-1,4-benzoxazines and thia analogues are unique fused-bicyclic *N*-arylamines possessing a β-heteroatom, and are core structures in many useful biologically active compounds.[1,2] Asymmetric hydrogenation of 2-substituted quinoxalines,[3–6] 3-substituted 2*H*-1,4-benzoxazines,[7] and 3-substituted 2*H*-1,4-benzothiazines is among the most direct and reliable methods to produce these important molecules. Recently, several efficient procedures with chiral Ir and Ru catalysts have been reported for this reaction of quinoxalines.[5,6] The high activity of the $Ir(I)H_8$-BINAPO/I_2 catalyst system [substrate-to-catalyst molar ratio (S/C) 20,000, 48 atm of H_2, −5 °C, 20 h, 91% conversion, 93% enantiomeric excess (*ee*)][5e] and enantioselectivity as high as 99% using the Ru(II)(MsDPEN)(η^6-*p*-cymene) catalyst (S/C = 100, 50 atm of H_2, 40 °C, 8 h)[6d] are notable. Hydrogenation of 2*H*-1,4-benzoxazine substrates with chiral Ir catalysts (e.g., S/C = 200, 40 atm of H_2, room temperature, 20 h) afforded the products in up to 95% *ee*.[7] The biomimetic asymmetric reduction using a 9,10-dihydrophenanthridine/chiral Brønsted acid system (S/C = 100) followed by regeneration of the reductant *via* [RuI_2(*p*-cymene)]$_2$-catalyzed (S/C = 50, 3 atm of H_2, room temperature, 32 h) hydrogenation of phenanthridine gave the 3,4-dihydro-2*H*-1,4-benzoxazines in up to 92% *ee*.[6e] To the best of our knowledge, no asymmetric hydrogenation of 3-substituted 2*H*-1,4-benzothiazines has previously been reported.[8] Thus, the development of highly active and enantioselective catalysts for hydrogenation of these heterocyclic imines is a desirable objective.

We have recently reported an extremely rapid and enantioselective hydrogenation of ketones catalyzed by the RuCl(daipena)(xylbinap)/base (base: *t*-C_4H_9OK or DBU) system [XylBINAP = 2,2′-bis(di-3,5-xylylphosphino)-1,1′-binaphthyl: see the structure illustrated in Scheme 1].[9–11] The turnover frequency in the reaction of acetophenone (S/C = 100,000, 50 atm of H_2) reached as high as 350,000 min^{-1} producing 1-phenylethanol in >99% *ee*. The unique ruthenabicyclic structure of this complex with an Ru–C bond appears to be significant for achieving high activity. We expected that this new type of catalyst could be useful for the enantioselective hydrogenation of 2-substituted quinoxalines as well as 3-substituted 2*H*-1,4-benzoxazines and their thia analogues.

We first selected 2-methylquinoxaline (**1a**) as a typical substrate for optimization of the catalyst structure and the reaction conditions (Scheme 1 and Table 1). When **1a** (0.505 mmol) was hydrogenated in 2-propanol, a typical solvent for this catalyzed reaction, at



Scheme 1. Asymmetric hydrogenation of 2-methylquinoxaline (**1a**). R_N: *R* configuration of the nitrogen-containing ligand (DAIPEN or DAIPENA). R_P: *R* configuration of the phosphorus-containing ligand (SEGPHOS, DM-SEGPHOS, or XylBINAP).

25 °C under 20 atm of H_2 for 20 h in the presence of RuCl[(*R*)-daipena][(*R*)-dm-segphos] [(R_N,R_P)-**4a**][9,12,13] (2.6 μmol, S/C = 200) and *t*-C_4H_9OK (0.130 mmol), the desired (*S*)-1,2,3,4-tetrahydro-2-methylquinoxaline [(*S*)-**2a**] was obtained in 91% yield and 99% *ee* accompanied by the partially hydrogenated compound **3a** in 4% yield (entry 1). The yield and enantiomeric purity of **2a** decreased on using RuCl(daipena)(xylbinap) (**5**) or $RuCl_2$(dm-segphos)-(daipen) (**6**), both of which exhibit excellent catalytic performance in the reaction of ketones, instead of **4a** (entries 2 and 3).[9,10] The electron-donating ability of DM-SEGPHOS and the ruthenabicyclic structure with a Ru–C (aryl) bond appear to be important for achieving higher activity and enantioselectivity. Only partially hydrogenated compound **3a** in 56% yield was observed in the hydrogenation with **4a** in methanol under otherwise identical conditions (entry 4). The reaction in ethanol, *tert*-butyl alcohol or THF gave **2a** in approximately 90% yield and >99% *ee* contaminated by a small amount of **3a** (entries 5–7). When the hydrogenation was carried out in CH_2Cl_2 or toluene, the desired product **2a** was obtained in 90% and 94% yields, respectively, as a sole compound (entries 8 and 9). Thus, we selected toluene as the most preferable solvent. The reaction rate increased at 40 °C, resulting in complete conversion to **2a** without a loss of enantioselectivity (entry 10). A high yield of 90% was obtained in the reaction with an S/C of 100 even under 1–1.5 atm of H_2 for 28 h (entry 11). The substrate **1a** was completely transformed into **2a** in the hydrogenation with an S/C of 2000 under 20 atm of H_2 for 21 h (entry 14). A turnover number of ap-

Table 1. Asymmetric hydrogenation of 2-methylquinoxaline (**1a**) catalyzed by chiral Ru complexes.[a]

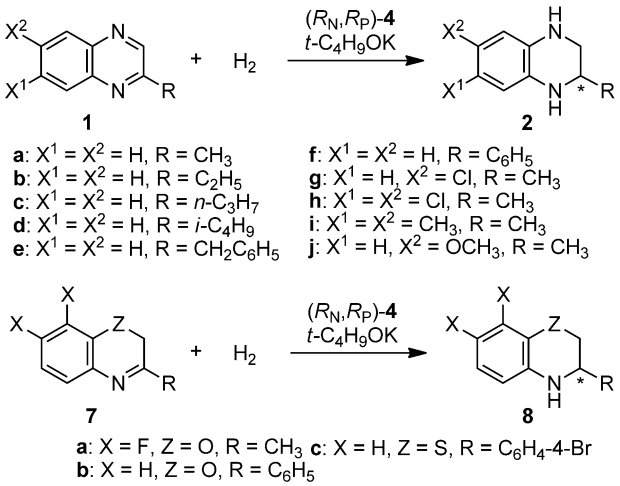
Entry	Catalyst	S/C[b]	Solvent	Temperature [°C]	Time [h]	Yield of **2a**/**3a** [%][c]	*ee* of **2a** [%][d]
1	(R_N,R_P)-**4a**	200	*i*-PrOH	25	20	91/4	99
2	(S_N,S_P)-**5**	200	*i*-PrOH	25	22	89/3	95[e]
3	(R_N,R_P)-**6**	200	*i*-PrOH	25	19	35/33	93
4	(R_N,R_P)-**4a**	200	MeOH	25	21	<1/56	–
5	(R_N,R_P)-**4a**	200	EtOH	25	20	91/4	>99
6	(R_N,R_P)-**4a**	200	*t*-BuOH	25	20	89/4	>99
7	(R_N,R_P)-**4a**	200	THF	25	19	93/1	>99
8	(R_N,R_P)-**4a**	200	CH_2Cl_2	25	28	90/<1	>99
9	(R_N,R_P)-**4a**	200	toluene	25	21	94/<1	>99
10	(R_N,R_P)-**4a**	200	toluene	40	20	>99/<1	>99
11[f]	(R_N,R_P)-**4a**	100	toluene	40	28	90/<1	>99
12[g]	(R_N,R_P)-**4a**	1000	toluene	40	13	>99/<1	>99
13[g]	(R_N,R_P)-**4b**	1000	toluene	40	15	96/<1	94
14[g]	(R_N,R_P)-**4a**	2000	toluene	40	21	>99/<1	>99
15[h]	(R_N,R_P)-**4a**	8000	toluene	40	40	89/<1	>99

[a] Unless otherwise stated, reactions were carried out using **1a** (0.3–0.5 mmol) in solvent (0.7–2.5 mL) containing (R_N,R_P)-**4**, (S_N,S_P)-**5**, or (R_N,R_P)-**6** (2.4–3.6 μmol) and *t*-C_4H_9OK (0.12–0.18 mmol) under 20 atm of H_2.
[b] Substrate/catalyst molar ratio.
[c] Determined by ^1H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard.
[d] Data of (*S*)-**2a** determined by chiral GC or HPLC analysis.
[e] Data of (*R*)-**2a**.
[f] Reaction at 1–1.5 atm of H_2.
[g] Reaction using **1a** (2.3–5.0 mmol) with **4** (2.3–2.6 μmol) and *t*-C_4H_9OK (0.12–0.13 mmol).
[h] Reaction using **1a** (13.0 mmol) with **4a** (1.4 μmol) and *t*-C_4H_9OK (0.68 mmol) under 100 atm of H_2.

proximately 7100 was obtained in the reaction with an S/C of 8000 under 100 atm of H_2 for 40 h (entry 15). The bulky 3,5-xylyl groups on the phosphine ligand were crucial to achieving excellent enantioselectivity in the reaction of **1a**. Thus, the *ee* value decreased to 94% with the RuCl(daipena)(segphos) (**4b**: Ar = phenyl)[12] instead of **4a** (entry 12 *versus* 13). Consequently, the **4a**/*t*-C_4H_9OK catalyst system achieved both excellent activity and enantioselectivity in the hydrogenation of **1a**.[5]

The **4a**/*t*-C_4H_9OK catalyst system was applied to the asymmetric hydrogenation of a series of quinoxaline derivatives **1** (Table 2). The methyl-, ethyl-, and propyl-substituted compounds at the C-2 position (**1a**–**1c**) were quantitatively hydrogenated (S/C = 1000, 20 atm of H_2, 40 °C) to afford the 2-substituted 1,2,3,4-tetrahydroquinoxalines, **2a**–**2c**, in >99% *ee* (entries 1–3). The reaction of **1d** with a relatively bulky isobutyl group was somewhat slower, but the benzyl-substituted compound **1e** was smoothly converted to **2e** under the same conditions (entries 4 and 5). No hydrogenation of the 2-phenyl substrate **1f** occurred (entry 6), which may have been due to the bulkiness of the phenyl group. Fortunately, the hydrogenation of **1f** proceeded by using RuCl[(*R*)-daipena][(*R*)-segphos] [(R_N,R_P)-**4b**] with an S/C of 100, resulting in the *R* (not *S*) enantiomer of **2f** in 96% *ee* quantitatively (entry 7). The mode of enantioselection will be discussed below. The 6-chloro and 6,7-dichloro-2-methylquinoxalines, **1g** and **1h**, were

Table 2. Asymmetric hydrogenation of quinoxalines **1**, benzoxazines **7a**, **b**, and a benzothiazine **7c** with the ruthenabicyclic complex **4**.[a]



Entry	Substrate	Catalyst	S/C[b]	Time [h]	Yield [%][c]	*ee* [%][d]
1	**1a**	**4a**	1000	13	>99 (>99)	>99 (*S*)
2	**1b**	**4a**	1000	25	99 (96)	>99 (*S*)
3	**1c**	**4a**	1000	28	>99 (96)	>99 (*S*)
4	**1d**	**4a**	1000	31	89 (82)	97 (*S*)
5	**1e**	**4a**	1000	29	99 (96)	98 (*S*)
6	**1f**	**4a**	100	24	<1	–
7	**1f**	**4b**	100	16	>99 (99)	96 (*R*)
8	**1g**	**4a**	200	16	>99 (97)	>99 (*S*)
9	**1h**	**4a**	200	16	>99 (95)	98 (*S*)
10[e]	**1h**	**4a**	9400	72	>99 (97)	>99 (*S*)
11	**1i**	**4a**	100	23	>99 (97)	>99 (*S*)
12	**1j**	**4a**	100	24	>99 (99)	>99 (*S*)
13	**7a**	**4a**	200	23	>99 (98)	98 (*S*)
14	**7b**	**4b**	200	22	>99 (99)	98 (*R*)
15	**7c**	**4b**	100	36	>99 (98)	>99 (*R*)

[a] Unless otherwise stated, reactions were carried out using **1** or **7** (0.1–2.0 mmol) in toluene with (R_N,R_P)-**4** and *t*-C_4H_9OK under 20 atm of H_2 at 40 °C. **4**:*t*-C_4H_9OK = 1:50.
[b] Substrate/catalyst molar ratio.
[c] Determined by ^1H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard. Isolated yield is given in parentheses.
[d] Determined by chiral HPLC analysis. Absolute configuration of the product is stated in parentheses.
[e] Reaction using **1h** (8.0 mmol) under 100 atm of H_2.

quantitatively hydrogenated (S/C = 200, 20 atm of H_2) to the tetrahydro products **2g** and **2h** in >99% *ee* and 98% *ee*, respectively (entries 8 and 9). The high reactivity of **1h** resulted in complete conversion in the hydrogenation with an S/C of 9400 under 100 atm of H_2 in 72 h to yield **2h** in >99% *ee* (entry 10). The substitution with the electron-donating methyl or methoxy group at the 6 and 7 positions, **1i** and **1j**, decreased the reaction rate, but the high level of enantioselectivity was maintained (entries 11 and 12). The products **2i** and **2j** were readily oxidized back to the substrates **1i** and **1j** in open air, causing difficulty in separating these products from the substrates. We therefore isolated **2i** and **2j** merely by passing the reaction mixture through a silica gel pad to remove the metallic contents.

The (R_N,R_P)-**4a**/*t*-C_4H_9OK system also efficiently catalyzed asymmetric hydrogenation of 7,8-difluoro-3-methyl-2*H*-1,4-benzoxazine (**7a**). The reaction with an S/C of 200 was completed in 23 h to afford (*S*)-**8a** in 98% *ee* (Table 2, entry 13). The product (*S*)-**8a** is a key intermediate for the synthesis of the antibacterial agent levofloxacin.[2c,7a] The 3-aryl-substituted benzoxazine and benzothiazine compounds, **7b** and **7c**, were hydrogenated with the (R_N,R_P)-**4b**/*t*-C_4H_9OK catalyst to yield (*R*)-**8b** and (*R*)-**8c** in 98% *ee* and >99% *ee*, respectively (entries 14 and 15). The senses of enantioselectivity were consistent with that of the reaction of the phenyl-substituted quinoxaline **1f** (see entry 7).

Our recent mechanistic studies on the asymmetric hydrogenation of ketones catalyzed by the ruthenabicyclic complexes **4** with base revealed that the hydride complex RuH(daipena)(diphosphine) (diphosphine = DM-SEGPHOS, XylBINAP) was formed under the reaction conditions.[9,14] This RuH complex is expected to act as the reactive species in the hydrogenation of the heterocyclic imines, **1** and **7**. Figure 1 illustrates molecular models of RuH[(*R*)-daipena][(*R*)-dm-segphos] [(R_N,R_P)-RuH] based on the X-ray structure of the RuCl precursor (R_N,R_P)-**4a** that was previously reported by our group.[9] The structure is fixed by the ruthenabicyclo[2.2.1] skeleton. The benzylic amine axial-proton (H_{ax}) of the complex is the most reactive among the four amine protons, because the H–Ru–N–H_{ax} torsion angle is expected to be the smallest.[15] The hydrogenation of **3a**, which is the second step of the reaction of **1a**, proceeds through the six-membered pericyclic transition state, $\mathbf{TS_A}$ or $\mathbf{TS_B}$, in which the planar arranged $H^{\delta-}$–$Ru^{\delta+}$–$N^{\delta-}$–$H_{ax}{}^{\delta+}$ quadrupole of the catalyst fits well with the $C^{\delta+}$=$N^{\delta-}$ dipole of the substrate (metal-ligand cooperative TS).[10,16] $\mathbf{TS_B}$ suffers significant non-bonded repulsion between the fused arene ring of the substrate and the 3,5-xylyl moieties of the catalyst. Therefore, (*S*)-**2a** is exclusively produced through the $\mathbf{TS_A}$. The rigid chiral envi-

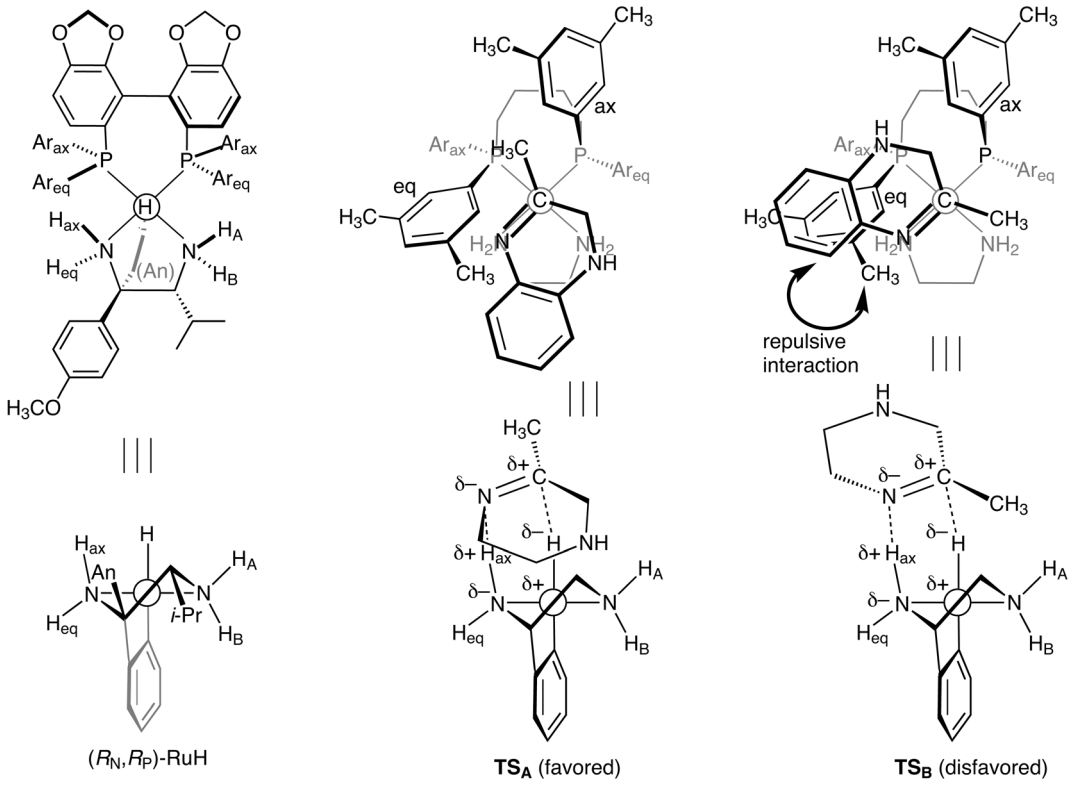


Figure 1. Structure of (R_N,R_P)-RuH species derived from **4a** and diastereomeric transition states in the second step of hydrogenation of **1a**. Some aromatic groups and substituents are omitted for clarity. An = 4-anisyl, Ar = 3,5-xylyl, *i*-Pr = isopropyl.

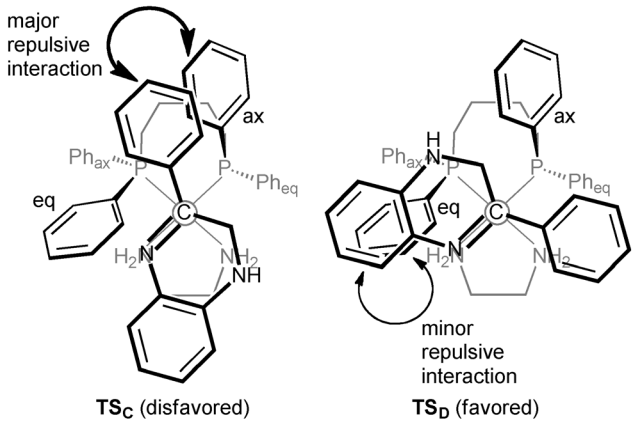


Figure 2. Molecular models of diastereomeric transition states in the second step of hydrogenation of **1f** with (R_N,R_P)-**4b**. Some aromatic groups and substituents are omitted for clarity.

ronment of the ruthenabicyclic catalyst appears to be effective for achieving high enantioselectivity.

On the other hand, the hydrogenation of **3f** derived from **1f** with the (R_N,R_P)-**4b**/*t*-C_4H_9OK catalyst preferably proceeds through the $\mathbf{TS_D}$ over the $\mathbf{TS_C}$ to selectively produce (*R*)-**2f** (Figure 2), as the steric repulsion between the 2-phenyl group of the substrate and the P-phenyl$_{(ax)}$ moiety of the catalyst in $\mathbf{TS_C}$ is much greater than that between the fused arene ring of the substrate and the P-phenyl$_{(eq)}$ moiety of the catalyst in $\mathbf{TS_D}$.

In summary, RuCl[(*R*)-daipena][(*R*)-dm-segphos] [(R_N,R_P)-**4a**] with *t*-C_4H_9OK exhibits high catalytic activity and enantioselectivity for hydrogenation of 2-alkylquinoxalines **1** and a 3-methyl-2*H*-1,4-benzoxazine **7a** in toluene, affording the heterocyclic amines (*S*)-**2** and (*S*)-**8a** in >97% *ee*. A turnover number of as high as 9400 is achieved for the catalyst. The less hindered RuCl[(*R*)-daipena][(*R*)-segphos] [(R_N,R_P)-**4b**]/*t*-C_4H_9OK system efficiently catalyzes the hydrogenation of the benzoimine heterocycles, **1f**, **7b**, and **7c**, to yield the *R* products in high *ee*. The mode of enantioselection is interpreted by using transition state models involving six-membered pericyclic structures.

Experimental Section

Typical Procedure for the Asymmetric Hydrogenation of 1a with (R_N,R_P)-4a

The ruthenium complex (R_N,R_P)-**4a** (1.0 mg, 0.85 μmol) and *t*-BuOK (4.4 mg, 0.039 mmol) were placed in a 100-mL glass autoclave filled with argon. The reaction vessel was evacuated and refilled with argon. A solution of freshly distilled 2-methylquinoxaline (**1a**) (122.8 mg, 0.852 mmol) in toluene (0.85 mL) that had been degassed by three freeze-thaw cycles was transferred to the autoclave through a Teflon cannula. Hydrogen was initially introduced into the autoclave at a pressure of 8 atm before being reduced to 1 atm. This procedure was repeated ten times. The autoclave was then pressurized with H_2 gas (20 atm), and the solution was stirred vigorously at 40 °C for 13 h. After careful release of the hydrogen, the solution was concentrated under reduced pressure. The crude material was filtered through a short pad of silica gel by eluting with hexane:ethyl acetate (1:1), to give (*S*)-1,2,3,4-tetrahydo-2-methylquinoxaline [(*S*)-**2a**] as a yellowish-white solid; yield: 126.1 mg (0.851 mmol, 99.9%, 99.8% *ee*); $[\alpha]_D^{25}$: −33.8 (*c* 1.06, EtOH), lit.,[5k] $[\alpha]_D^{24}$: −20.1 (*c* 0.87, EtOH, for *S* enantiomer with 76% *ee*). IR (KBr): ν = 3352, 3315, 2959, 2875, 1603, 1519, 1308, 741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 1.19 (d, *J* = 6.3 Hz, 3H), 3.04 (dd, *J* = 10.8, 8.1 Hz, 1H), 3.32 (dd, *J* = 10.8, 2.7 Hz, 1H), 3.50–3.56 (m, 1H), 3.60 (br s, 2H), 6.49–6.53 (m, 2H), 6.56–6.60 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.9 (CH_3), 45.6 (CH), 48.2 (CH_2), 114.35 (CH), 114.40 (CH), 118.6 (CH × 2), 133.1 (C), 133.5 (C). The enantiomeric excess of **2a** was determined by HPLC analysis [column, CHIRALCEL OD-H (4.6 × 250 mm); eluent, hexane:*i*-PrOH = 80:20; flow, 0.5 mL min^{-1}; detector: UV 254 nm; column temp, 40 °C]: t_R of (*R*)-**2a**, 16.1 min (0.1%); t_R of (*S*)-**2a**, 18.4 min (99.9%), lit.,[5d] t_R of (*R*)-**2a**, 16.5 min; t_R of (*S*)-**2a**, 19.0 min.

Acknowledgements

This work was supported by a Grant-in-Aid from the Japan Society for the Promotion of Science (JSPS) (No. 24350042) and the MEXT (Japan) program "Strategic Molecular and Materials Chemistry through Innovative Coupling Reactions" of Hokkaido University.

References

[1] For examples of 2-substituted 1,2,3,4-tetrahydroquinoxalines, see: a) E. J. Jacobsen, L. S. Stelzer, K. L. Belonga, D. B. Carter, W. B. Im, V. H. Sethy, A. H. Tang, P. F. VonVoigtlander, J. D. Petke, *J. Med. Chem.* **1996**, *39*, 3820–3836; b) Y. Ohtake, A. Naito, H. Hasegawa, K. Kawano, D. Morizono, M. Taniguchi, Y. Tanaka, H. Matsukawa, K. Naito, T. Oguma, Y. Ezure, Y. Tsuriya, *Bioorg. Med. Chem.* **1999**, *7*, 1247–1254; c) K. Torisu, K. Kobayashi, M. Iwahashi, Y. Nakai, T. Onoda, T. Nagase, I. Sugimoto, Y. Okada, R. Matsumoto, F. Nanbu, S. Ohuchida, H. Nakai, M. Toda, *Bioorg. Med. Chem.* **2004**, *12*, 5361–5378; d) J. A. Sikorski, *J. Med. Chem.* **2006**, *49*, 1–22; e) C. T. Eary, Z. S. Jones, R. D. Groneberg, L. E. Burgess, D. A. Mareska, M. D. Drew, J. F. Blake, E. R. Laird, D. Balachari, M. O'Sullivan, A. Allen, V. Marsh, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2608–2613.

[2] For examples of 3-substituted 3,4-dihydro-2*H*-1,4-benzoxazines, see: a) K. S. Brown Jr, C. Djerassi, *J. Am. Chem. Soc.* **1964**, *86*, 2451–2463; b) I. Hayakawa, S. Atarashi, S. Yokohama, M. Imamura, K. Sakano, M. Furukawa, *Antimicrob. Agents Chemotherap.* **1986**, *29*, 163–164; c) S. Atarashi, S. Yokohama, K. Yamazaki, K. Sakano, M. Imamura, I. Hayakawa, *Chem. Pharm. Bull.* **1987**, *35*, 1896–1902; d) J.-Y. Shim, E. R. Collantes, W. J. Welsh, *J. Med. Chem.* **1998**, *41*, 4521–4532;

e) S. D. McAllister, G. Rizvi, S. Anavi-Goffer, D. P. Hurst, J. Barnett-Norris, D. L. Lynch, P. H. Reggio, M. E. Abood, *J. Med. Chem.* **2003**, *46*, 5139–5152; f) J. Ilaš, P. Š. Anderluh, M. S. Dolenc, D. Kikelj, *Tetrahedron* **2005**, *61*, 7325–7348.

[3] Recent review: D.-S. Wang, Q.-A. Chen, S.-M. Lu, Y.-G. Zhou, *Chem. Rev.* **2012**, *112*, 2557–2590.

[4] For Rh(I)-catalyzed hydrogenation, see: a) S. Murata, T. Sugimoto, S. Matsuura, *Heterocycles* **1987**, *26*, 763–766; b) H. Brunner, P. Bublak, M. Helget, *Chem. Ber.* **1997**, *130*, 55–61; c) H. Brunner, S. Rosenboem, *Monatsh. Chem.* **2000**, *131*, 1371–1382.

[5] For Ir(I)-catalyzed hydrogenation, see: a) C. Bianchini, P. Barbaro, G. Scapacci, E. Farnetti, M. Graziani, *Organometallics* **1998**, *17*, 3308–3310; b) C. Bianchini, P. Barbaro, G. Scapacci, *J. Organomet. Chem.* **2001**, *621*, 26–33; c) L. Qiu, F. Y. Kwong, J. Wu, W. H. Lam, S. Chan, W.-Y. Yu, Y.-M. Li, R. Guo, Z. Zhou, A. S. C. Chan, *J. Am. Chem. Soc.* **2006**, *128*, 5955–5965; d) N. Mršić, T. Jerphagnon, A. J. Minnaard, B. L. Feringa, J. G. de Vries, *Adv. Synth. Catal.* **2009**, *351*, 2549–2552; e) W. Tang, L. Xu, Q.-H. Fan, J. Wang, B. Fan, Z. Zhou, K. Lam, A. S. C. Chan, *Angew. Chem.* **2009**, *121*, 9299–9302; *Angew. Chem. Int. Ed.* **2009**, *48*, 9135–9138. H_8-BINAPO = 5,5′,6,6′,7,7′,8,8′-octahydro(1,1′-binaphthalene)-2,2′-diyl diphenylphosphinite; f) D. Cartigny, T. Nagano, T. Ayad, J.-P. Genêt, T. Ohshima, K. Mashima, V. Ratovelomanana-Vidal, *Adv. Synth. Catal.* **2010**, *352*, 1886–1891; g) D.-S. Wang, Y.-G. Zhou, *Tetrahedron Lett.* **2010**, *51*, 3014–3017; h) J. L. Núñez-Rico, H. Fernández-Pérez, J. Benet-Buchholz, A. Vidal-Ferran, *Organometallics* **2010**, *29*, 6627–6631; i) D. Cartigny, F. Berhal, T. Nagano, P. Phansavath, T. Ayad, J.-P. Genêt, T. Ohshima, K. Mashima, V. Ratovelomanana-Vidal, *J. Org. Chem.* **2012**, *77*, 4544–4556; j) T. Nagano, A. Iimuro, R. Schwenk, T. Ohshima, Y. Kita, A. Togni, K. Mashima, *Chem. Eur. J.* **2012**, *18*, 11578–11592; k) D.-W. Wang, D.-S. Wang, Q.-A. Chen, Y.-G. Zhou, *Chem. Eur. J.* **2010**, *16*, 1133–1136.

[6] For Ru(II)-catalyzed hydrogenation, see: a) C. J. Cobley, J. P. Henschke, *Adv. Synth. Catal.* **2003**, *345*, 195–201; b) J. P. Henschke, M. J. Burk, C. G. Malan, D. Herzberg, J. A. Peterson, A. J. Wildsmith, C. J. Cobley, G. Casy, *Adv. Synth. Catal.* **2003**, *345*, 300–307; c) Q.-A. Chen, D.-S. Wang, Y.-G. Zhou, Y. Duan, H.-J. Fan, Y. Yang, Z. Zhang, *J. Am. Chem. Soc.* **2011**, *133*, 6126–6129; d) J. Qin, F. Chen, Z. Ding, Y.-M. He, L. Xu, Q.-H. Fan, *Org. Lett.* **2011**, *13*, 6568–6571. MsDPEN = *N*-(methanesulfonyl)-1,2-diphenylethylenediamine; e) Q.-A. Chen, K. Gao, Y. Duan, Z.-S. Ye, L. Shi, Y. Yang, Y.-G. Zhou, *J. Am. Chem. Soc.* **2012**, *134*, 2442–2448.

[7] a) K. Satoh, M. Inenaga, K. Kanai, *Tetrahedron: Asymmetry* **1998**, *9*, 2657–2662; b) K. Gao, C.-B. Yu, D.-S. Wang, Y.-G. Zhou, *Adv. Synth. Catal.* **2012**, *354*, 483–488; c) J. L. Núñez-Rico, A. Vidal-Ferran, *Org. Lett.* **2013**, *15*, 2066–2069.

[8] For chiral Brønsted acid-catalyzed asymmetric transfer hydrogenation of 3-substituted 2*H*-1,4-benzothiazines with Hantzsch dihydropyridine, see: M. Rueping, A. P. Antonchick, T. Theissmann, *Angew. Chem.* **2006**, *118*, 6903–6907; *Angew. Chem. Int. Ed.* **2006**, *45*, 6751–6755.

[9] K. Matsumura, N. Arai, K. Hori, T. Saito, N. Sayo, T. Ohkuma, *J. Am. Chem. Soc.* **2011**, *133*, 10696–10699.

[10] For selected reviews for asymmetric hydrogenation catalyzed by diphosphine/diamine–Ru(II) complexes, see: a) T. Ohkuma, *Proc. Jpn. Acad. Ser. B* **2010**, *86*, 202–219; b) T. Ohkuma, *J. Synth. Org. Chem. Jpn.* **2007**, *65*, 1070–1080; c) R. Noyori, T. Ohkuma, *Angew. Chem.* **2001**, *113*, 40–75; *Angew. Chem. Int. Ed.* **2001**, *40*, 40–73.

[11] Asymmetric hydrogenation of imines with diphosphine/diamine–Ru(II) catalysts: N. Arai, N. Utsumi, Y. Matsumoto, K. Murata, K. Tsutsumi, T. Ohkuma, *Adv. Synth. Catal.* **2012**, *354*, 2089–2095. See also refs.[6a,6b]

[12] DM-SEGPHOS and SEGPHOS: a) T. Saito, T. Yokozawa, T. Ishizaki, T. Moroi, N. Sayo, T. Miura, H. Kumobayashi, *Adv. Synth. Catal.* **2001**, *343*, 264–267; b) H. Shimizu, I. Nagasaki, K. Matsumura, N. Sayo, T. Saito, *Acc. Chem. Res.* **2007**, *40*, 1385–1393.

[13] The absolute configuration of the carbon center connected with 4-anisyl group in (R_N,R_P)-**4a** was determined to be *S* by X-ray analysis. See ref.[9] for details.

[14] RuH[(*R*)-daipena][(*R*)-binap] with a *cis*-RuH(arene) structure was prepared from RuH_2[(*R*)-binap][(*R*)-daipen] in hexane. See: K. Abdur-Rashid, A. J. Lough, *Acta Crystallogr.* **2012**, *E68*, m1486–m1487.

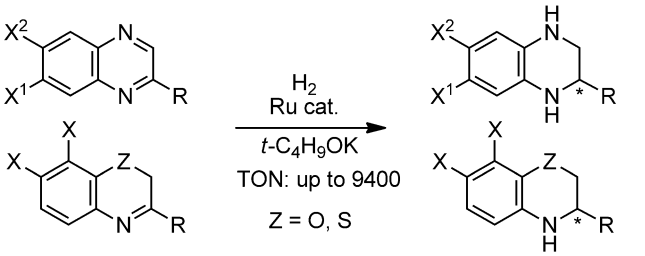
[15] The Cl–Ru–N–H_{ax} torsion angle of **4a** was determined to be 1.5° by the X-ray analysis. See ref.[9] for details.

[16] a) C. A. Sandoval, T. Ohkuma, K. Muñiz, R. Noyori, *J. Am. Chem. Soc.* **2003**, *125*, 13490–13503; b) C. A. Sandoval, T. Ohkuma, N. Utsumi, K. Tsutsumi, K. Murata, R. Noyori, *Chem. Asian J.* **2006**, *1–2*, 102–110. See also: c) K. Abdur-Rashid, S. E. Clapham, A. Hadzovic, J. N. Harvey, A. J. Lough, R. H. Morris, *J. Am. Chem. Soc.* **2002**, *124*, 15104–15118.

Asymmetric Hydrogenation of Quinoxalines, Benzoxazines, and a Benzothiazine Catalyzed by Chiral Ruthenabicyclic Complexes

Adv. Synth. Catal. **2013**, *355*, 1 – 7

Noriyoshi Arai, Yu Saruwatari, Kotaro Isobe, Takeshi Ohkuma*



Ru cat. = RuCl[(*R*)-daipena][(*R*)-(dm-)segphos]

7

