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Amine-Tunable Ruthenium Catalysts for Asymmetric Reduction of Ketones

Sonia Rodríguez,[a,*] Bo Qu,[a] Keith R. Fandrick,[a] Frederic Buono,[a] Nizar Haddad,[a] Yibo Xu,[a] Melissa A. Herbage,[a] Xingzhong Zeng,[a] Shengli Ma,[a] Nelu Grinberg,[a] Heewon Lee,[a] Zhengxu S. Han,[a] Nathan K. Yee,[a] and Chris H. Senanayake[a]

[a] Chemical Development US, Boehringer Ingelheim Pharmaceuticals, Inc., 900 Ridgebury Rd, Ridgefield, CT 06877, USA
E-mail: sonia.rodriguez@boehringer-ingelheim.com

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Abstract: A series of efficient ruthenium catalysts has been developed for the asymmetric hydrogenation and transfer hydrogenation of ketones with high reactivities and selectivities. The new chiral bisdihydrobenzooxaphosphole (BIBOP)/diamine-ruthenium complexes catalyzed the enantioselective hydrogenation of substrates such as aryl and heteroaryl cyclic and alkyl ketones with substrate/catalyst (S/C) ratios of up to 100,000. The opposite sense of enantioselectivity can be obtained by proper selection of a diamine with a given chirality of the phosphine. The usefulness of the new system has been demonstrated in the asymmetric hydrogenation of a complex synthetic intermediate towards cholesteryl ester transfer protein (CETP) inhibitors at S/C 20,000 on large-scale operation.

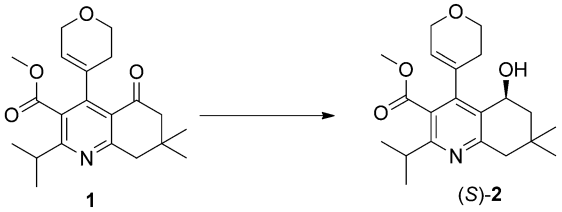
Keywords: asymmetric hydrogenation; asymmetric transfer hydrogenation; bisdihydrobenzooxaphosphole (BIBOP) ligands; phosphorus ligands; ruthenium

The asymmetric reduction of ketones is a key transformation in the pharmaceutical industry for the preparation of enantiomerically pure alcohols, particularly those bearing heterocycles.[1] Chiral $RuCl_2$(diphosphine)(diamine) complexes pioneered by Noyori and co-workers catalyze the highly efficient asymmetric hydrogenation of a wide array of ketones to afford the corresponding alcohols.[2] Despite the variety of catalysts described in the literature[3] very few ruthenium catalysts have been able to hydrogenate cyclic ketones such as 1-tetralones.[3l,4] Furthermore, examples of the hydrogenation of heteroaryl cyclic ketones are extremely rare. To the best of our knowledge, the only reported asymmetric hydrogenations of heteroaryl cyclic ketones utilized a Ru-BINAP complex with a 1,4-diamine derived from natural mannitol for the reduction of 4,5,6,7-tetrahydrobenzofuran-4-one[4b] or η^6-arene/*N*-tosylethylenediamine-ruthenium(II) catalysts for the reduction of 4-chromanones.[5]

Some chiral catalysts have been reported to exhibit turnover numbers (TON, molar ratio of converted substrate to catalyst) over 100,000 with simple aryl methyl ketones,[2b,c,3l,6] but most of the reported chiral catalysts have TON lower than 1000, making these catalytic systems unsuitable for industrial applications.[7]

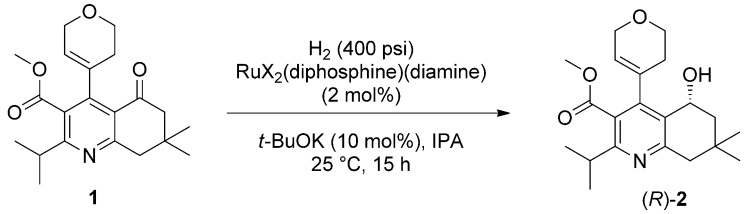
Herein, we disclose a new family of amine-tunable ruthenium catalysts based on chiral bisdihydrobenzooxaphosphole ligands (BIBOP ligands) as effective catalysts for the asymmetric hydrogenation and transfer hydrogenation of a variety of highly challenging ketones, including heteroaryl cyclic ketones. The reaction is conducted with TON values as high as 100,000 under 400 psi of hydrogen. The hydrogenation of a sterically hindered synthetic intermediate of a drug candidate, catalyzed by a Ru-BIBOP complex, was performed with S/C 20,000 in >99:1 *er*.

In the synthesis of potential cholesteryl ester transfer protein (CETP) inhibitors, we needed to perform the asymmetric reduction of ketone **1** (Scheme 1). The reduction of **1** was initially conducted with one equivalent of borane-diethylaniline and 15–20 mol%



Scheme 1. Asymmetric hydrogenation of ketone **1** towards CETP inhibitors.

Table 1. Evaluation of commercial Ru complexes for the asymmetric hydrogenation of **1**. Enantiomeric ratios were determined by chiral HPLC; The *R* absolute configuration of **2** was determined by chemical correlation to the final product.



Entry	Ru complex	Conversion [%][a]	*er*[b]
1	$RuCl_2$[(*R*)-BINAP][(*R*)-daipen]	11	–
2	$RuCl_2$[(*R*)-Xyl-BINAP][(*R*)-daipen]	23	5:95
3	$RuCl_2$[(*R*)-BINAP][(*R,R*)-dpen]	6	–
4	$RuCl_2$[(*S*)-Tol-BINAP][(*S*)-*i*-Pr-BIMAH]	100	98:2
5	$RuBr_2$[(*S*)-Xyl-Skewphos](ampy)	96	8:92
6	$RuCl_2$[(*R*)-Xyl-Phanephos][(*S,S*)-dpen]	0	–
7	$RuCl_2$[(*S*)-Xyl-P-Phos][(*R*)-daipen]	1	–
8	$RuCl_2$[(*S*)-Paraphos][(*R,R*)-dpen]	100	79:21
9	$RuCl_2$[(*S,S*)-DIOP][(*S*)-*i*-Pr-BIMAH]	98	26:74
10	(*R*)-RUCY^{TM}-Xyl-BINAP	10	17:83
11[c]	$RuCl_2$[(*S*)-Tol-BINAP](ampy)	100	98:2

[a] Molar conversion as determined by HPLC.
[b] Recorded as *R*:*S*.
[c] EtOH as solvent.

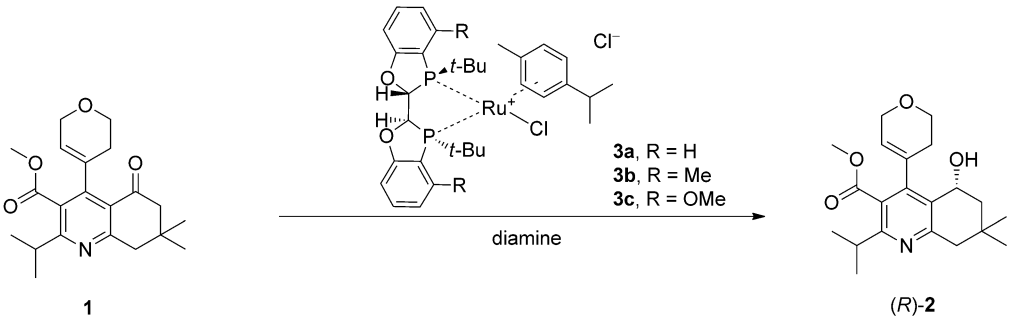
(1*R*,2*S*)-*cis*-1-amino-2-indanol to afford an 84% yield of (*S*)-**2** in 96:4 *er* on a multi-kilogram scale. Although the reaction performed well on scale-up, a greener and more efficient catalytic method was desired. To this end, the hydrogenation of ketone **1** was evaluated using 32 commercially available $RuCl_2$(diphosphine)-(diamine) complexes (S/C 50) with *t*-BuOK in isopropyl alcohol (IPA) (see the Supporting Information). This initial screen identified $RuCl_2$[(*S*)-tol-BINAP][(*S*)-*i*-Pr-BIMAH] {*i*-Pr-BIMAH = 2-[α-(isopropyl)-methanamine]-1*H*-benzimidazole} as a suitable catalyst for the reduction of **1** providing (*R*)-**2** in quantitative yield and 98:2 *er* (Table 1). Additional screening of solvents revealed $RuCl_2$[(*S*)-tol-BINAP](ampy) (ampy = 2-aminomethylpyridine) in ethanol as another active catalytic system, affording (*R*)-**2** in quantitative yield and 98:2 *er*. However, upon catalyst loading optimization studies, complete conversion was not achieved at S/C ≥ 1000, which was not economically feasible for scale-up due to the high cost of the catalysts.

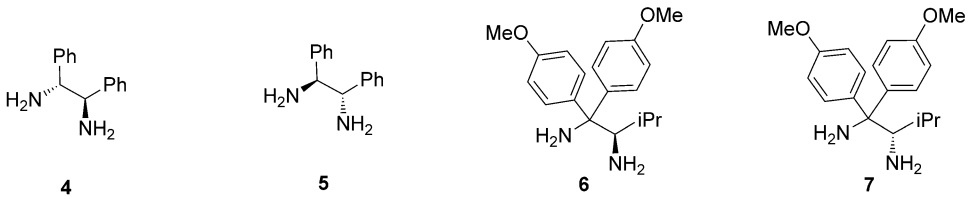
At this point, the reaction was evaluated using BIBOP ligands, which we had previously developed for rhodium-catalyzed hydrogenation of functionalized olefins.[8] $RuCl_2$(BIBOP)(*p*-cymene) complexes **3** were prepared from BIBOP and $[RuCl_2(p\text{-cymene})]_2$ in EtOH/CH_2Cl_2. To evaluate the efficiency of the new catalytic system, the hydrogenation of **1** was explored *in situ* with several diamines (Table 2). The highest enantioselectivities (over 99:1 *er*) were observed with 2-aminomethylpyridine (ampy), **8**, 2-aminomethylpyrimidine, **9**, and 8-aminoquinoline (amqui), **12**. Interestingly, the inverse enantioselectivity was observed when changing the R substituent in the BIBOP ligand from hydrogen (**3a**) or methyl (**3b**) to methoxy (**3c**) with **8** as diamine, going from 9:91 and 6:94 to > 99:1 *er*, respectively. Inverse selectivity effects were also observed with a given phosphine complex **3** and different amines, that is, **3c** provided opposite enantioselectivities with diamines **4** and **5** than **8**–**12**.

To evaluate the reactivity of the most selective catalysts for the reduction of **1**, we synthesized the corresponding $RuCl_2$(BIBOP)(diamine) complexes by reaction of **3** with the corresponding diamines in toluene at 110 °C. Isomeric mixtures of at least four isomers were observed by ^{31}P NMR spectroscopy when using diamines **8**, **9** and **12**.[9] As reported for other 2-aminomethylpyridine complexes, no differences in reactivity or enantioselectivity were observed regardless of the isomeric ratio of the pre-catalyst mixture.[3k,6b] Screening of the pre-made $RuCl_2$(MeO-BIBOP)-(diamine) catalysts along with optimization of the reaction conditions for solvent, pressure and temperature, allowed the synthesis of (*R*)-**2** using $RuCl_2$(MeO-BIBOP)(ampy), **13**, at S/C 20,000 under 300 psi of hydrogen on a 0.5 kg scale in 98% yield and > 99:1 *er*.

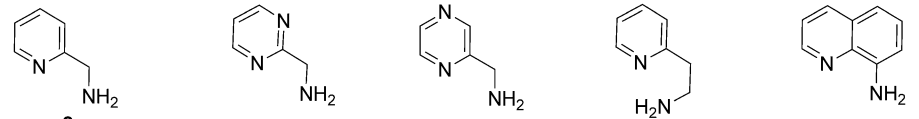
Hydrogenation of ketone **1** was monitored by FT-IR. Different amounts of purified product alcohol **2** (up to 100 mo%) were added at the beginning of the reaction and the decay of ketone **1** was recorded. A

Table 2. Evaluation of Ru-BIBOP/diamine complexes in the reduction of **1**.[a]





	4	5	6	7
3a:	0%	0%	0%	0%
3b:	0%	100%, 83:17	17%, 6:94	22%
3c:	100%, 46:54	79%, 26:74	6%	9%



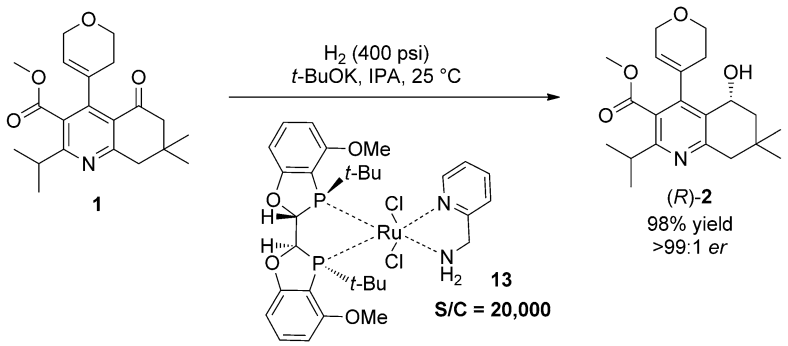
	8	9	10	11	12
3a:	100%, 9:91				
3b:	100%, 11:89				
3c:	100%, >99:1	100%, >99:1	25%, 99:1	47%, 92:8	100%, >99:1

[a] *Conditions:* H_2 (400 psi), 4–5 mol% precatalyst **3**, 4–5 mol% diamine, *t*-BuOK, *i*-PrOH, 25 °C, 15 h, molar conversion as determined by HPLC; *er* recorded as *R*:*S*.

first order simulation fits with the observed experimental data indicating a first order dependence of the reaction rate with the ketone concentration under the reaction conditions. The reaction rates with or without added product **2** were comparable, indicating a minor inhibiting effect of the product.

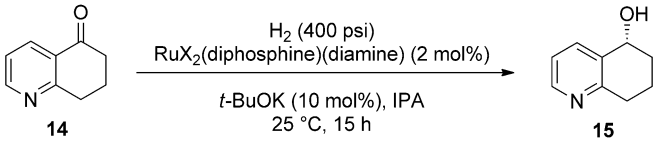
The prepared catalysts were also efficient for asymmetric transfer hydrogenation applications.[3g,10] When **1** was treated with 0.2 mol% **13** and 10 mol% sodium isopropoxide in IPA at 80 °C, a 93% yield of (*R*)-**2** and >99:1 *er* was obtained (Scheme 2).

The new Ru-BIBOP catalysts also proved to be more selective than 33 commercially available complexes in the reduction of 4,5,6,7,8-tetrahydro-5-quinolinone, **14** (see the Supporting Information and Table 3). Evaluation of commercial complexes allowed up to 92:8 er by using $RuCl_2$[(*S*)-Xyl-P-Phos][(*R*)-daipen] (entry 7). The highest enantioselectivities of >97:3 *er* were obtained when using complex **3c**



Scheme 2. Asymmetric hydrogenation of ketone **1**.

Table 3. Asymmetric hydrogenation of ketone **14**.



Entry	Ru complex	Conversion [%][a]	*er*[b]
1	$RuCl_2$[(*R*)-BINAP][(*R*)-daipen]	98	86:14
2	$RuCl_2$[(*R*)-Xyl-BINAP][(*R*)-daipen]	100	68:32
3	$RuCl_2$[(*R*)-BINAP][(*S,S*)-dpen]	100	12:88
4	$RuCl_2$[(*S*)-BINAP][(*S*)-*i*-Pr-BIMAH]	100	60:40
5	$RuBr_2$[(*S*)-Xyl-Skewphos][(*R*)-daipen]	100	87:13
6	$RuCl_2$[(*R*)-Xyl-Phanephos][(*S,S*)-dpen]	100	56:44
7	$RuCl_2$[(*S*)-Xyl-P-Phos][(*R*)-daipen]	100	92:8
8	$RuCl_2$[(*S*)-Paraphos][(*R,R*)-dpen]	100	49:51
9	$RuCl_2$[(*S,S*)-DIOP][(*S*)-*i*-Pr-BIMAH]	100	49:51
10	(*R*)-RUCY™-Xyl-BINAP	96	35:65
11	**3c+4**	100	1:99
12	**3c+5**	100	10:90
13	**3c+6**	100	5:95
14	**3c+7**	100	3:97
15	**3c+8**	100	59:41
16	**3c+12**	100	90:10

[a] Molar conversion determined by HPLC.
[b] Recorded as *R:S*.

with (*R,R*)-dpen, **4**, or (*S*)-daipen, **7** (entries 11 and 14). A remarkable inversion of the stereoselectivity was observed when using **3c** in combination with **12** (entry 16) instead of diamines **4–7** (entries 11–14). Although some scattered examples of inversion of stereoselectivity can be found in the literature, no general evaluation has been undertaken.[11]

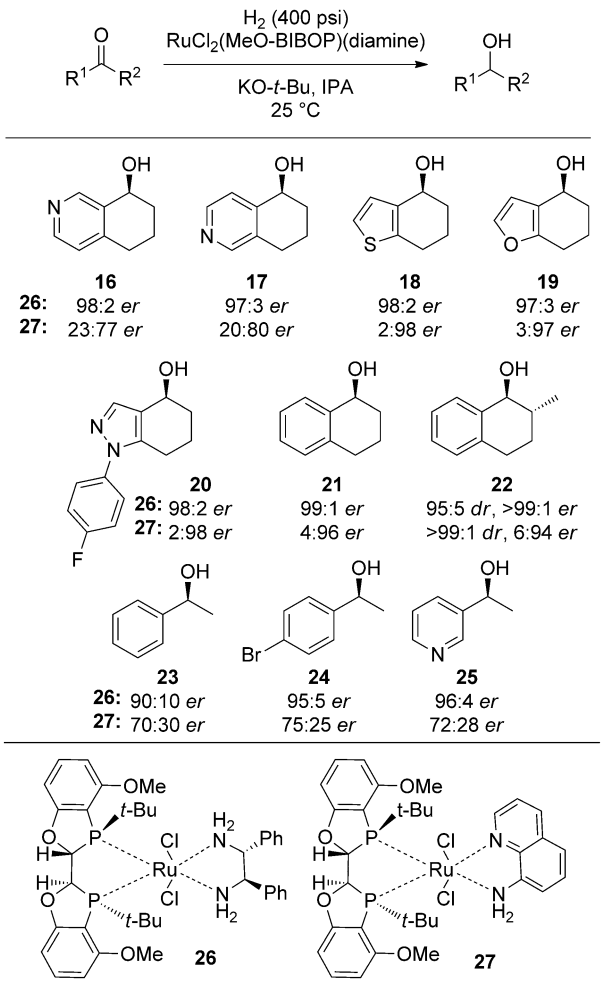
The reduction of other heterocycles to provide isoquinolines **16–17**, benzothiophene **18**, benzofuranone **19**, and pyrazole **20** also resulted in high selectivities (Table 4). Complete inversion of enantioselectivity was also observed in these cases using pre-made complexes **26** and **27**. These catalysts also provided high stereoselectivities of 1-tetralols **21–22**. In the case of indanones, high enantioselectivities but low isolated yields were obtained. Aryl alkyl ketones such as acetophenone, *p*-bromoacetophenone and 3-acetylpyridine were also suitable substrates providing **23–25** in relatively lower enantiomeric ratios of 90:10, 95:5 and 96:4, respectively, when using the dpen complex **26**.[12] Interestingly, in the case of the aryl methyl ketones, no inversion of enantioselectivity was observed when using the amqui complex **27**.

1-Tetralone, **28**, was selected as an inexpensive commercially available ketone to assess the reactivity of the newly developed catalysts (Scheme 3). (*S*)-1,2,3,4-Tetrahydro-1-naphthol, **21**, was obtained in 99% yield and 99:1 *er* when using **26** at S/C 100,000 under 400 psi of hydrogen and 60 °C. Analogously, the opposite enantiomer (*R*)-1,2,3,4-tetrahydro-1-naphthol, **29**, was obtained in 98% yield and 6:94 *er* when using **27** at S/C 100,000 under the same conditions.

In order to analyze the inverse stereoselectivity observed in the reduction of 1-tetralone, **28**, between catalysts **26** and **27**, computational studies utilizing density functional theory (DFT) using the *Gaussian 09* program[13] (B3LYP/LANL2DZ[14]) were conducted (Figure 1). Transition state optimizations were performed with the lowest energy binding mode for the Ru hydride complexes derived from **26** and **27** according to Noyori's postulated mechanism.[2f] The complex derived from pre-catalyst **26**, containing the dpen ligand **4**, is C_2 symmetrical and utilizing the axial hydrogen on the amine to complex the ketone orients the more sterically demanding side of the prochiral ketone away from the arene of the ligand framework. This, in turn, positions the *Re*-face of the ketone for hydride delivery producing the observed *S*-enantiomer of the substrate. In contrast, the transition state corresponding to the Ru hydride complex derived from **27**, containing the aminoquinoline ligand, positions the ketone on the opposite side of the complex as compared to the dpen catalyst. The arene unit of the substrate is then positioned away from the sterically demanding *tert*-butyl fragment of the ligand. This orientation exposes the *Si*-face of the prochiral ketone for hydride transfer generating the *R*-configuration of the secondary alcohol.

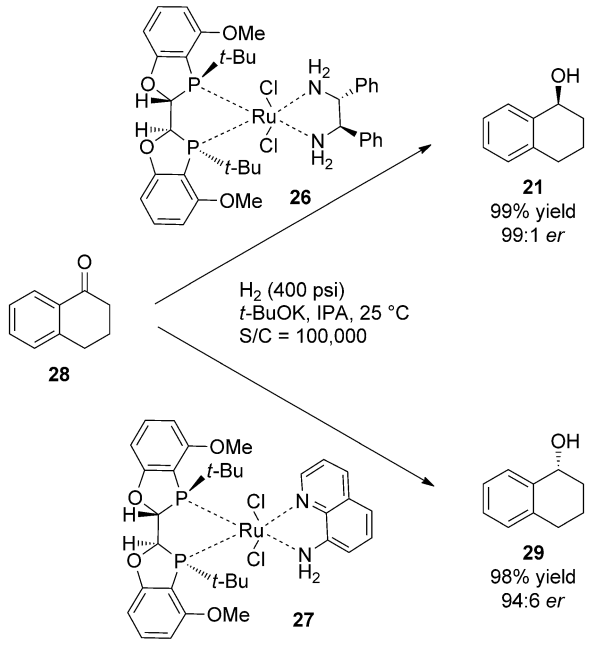
In summary, we have developed a series of novel and efficient ruthenium catalysts for asymmetric hy-

Table 4. Scope of the asymmetric hydrogenation.[a]



[a] *Reaction conditions:* 0.1–2 mol% $RuCl_2$(MeO-BIBOP)-(diamine), 0.2 equiv. *t*-BuOK, *i*-PrOH, room temperature, 20 h, 400 psi of hydrogen; The enantiomeric ratios were determined by chiral HPLC and refer to *S/R* ratios.

drogenation and transfer hydrogenation of ketones with high reactivities and excellent selectivities. The new chiral BIBOP/diamine-Ru complexes catalyzed the enantioselective hydrogenation of traditionally challenging substrates such as aryl and heteroaryl cyclic ketones as well as aryl and heteroaryl alkyl ketones with S/C up to 100,000. In addition, the opposite sense of enantioselectivity can be obtained by proper selection of a diamine with a given chirality of the phosphine. The usefulness of the new system has been demonstrated on the asymmetric hydrogenation of a complex synthetic intermediate towards CETP inhibitors at S/C 20,000 on large scale operation.



Scheme 3. Asymmetric hydrogenation of 1-tetralone, **28**.

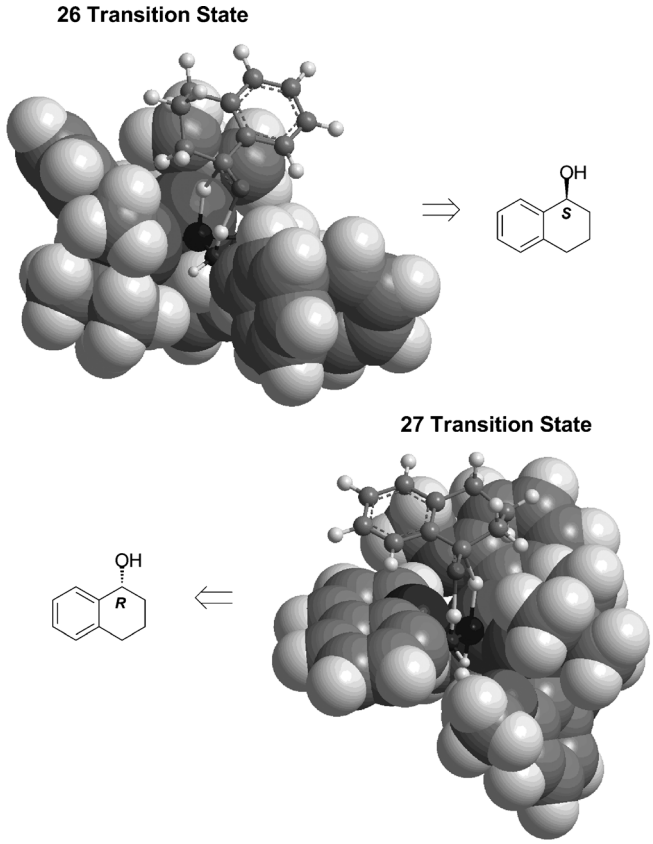


Figure 1. DFT (B3LYP/LANL2DZ) calculated transition states.

Experimental Section

General Procedure for Hydrogenation

Hydrogenation of **28** illustrates the typical reaction procedure. To a mixture of 1-tetralone, **28**, (10.0 g, 66.4 mmol) and $RuCl_2$[(2*R*,2′*R*,3*S*,3′*S*)-MeO-BIBOP](amqui), **27**, (1.0 mg, 0.001 mmol, 0.002 mol%) were added isopropyl alcohol (40 mL) and a 1 M solution of *t*-BuOK in *tert*-butyl alcohol (1.33 mL,1.33 mmol, 0.02 equiv.). The autoclave reactor was first purged with nitrogen, then with hydrogen, and then the reaction mixture was stirred at 60 °C under 400 psi of hydrogen for 20 h. After venting the hydrogen gas, the solvent was removed under reduced pressure. The residue was purified by silica-gel column chromatography with 0–50% ethyl acetate in hexane as eluent to give (*R*)-1,2,3,4-tetrahydro-1-naphthol, **29**, as a colorless oil; yield: 9.6 g (98%); 96:4 *er*. The *er* of 1,2,3,4-tetrahydro-1-naphthol was determined by HPLC analysis [column, Chiralcel OJ-3, 4.6 × 150 mm; eluent, heptane/isopropyl alcool (95:5); flow rate, 1 mL min^{-1}; column temperature, 25 °C]: retention time (t_R) of (*R*)-1,2,3,4-tetrahydro-1-naphthol, 7.45 min (95.8%); t_R of (*S*)-1,2,3,4-tetrahydro-1-naphthol, 5.75 min (4.2%); $[\alpha]_D$: −31.2 ($c = 2.0$, MeOH); literature[15] $[\alpha]_D^{23}$: −33.2° ($c = 1.0$, $CHCl_3$), >99% *ee* (*R*).

References

[1] a) *The Handbook of Homogeneous Hydrogenation*, (Eds.: J. G. De Vries, C. J. Elsevier), Willey-VCH, Weinheim, **2007**; b) C. Hedberg, in: *Modern Reduction Methods*, (Eds.: P. G. Andersson, I. J. Munslow), Wiley-VCH, Weinheim, **2008**, pp 109–134.

[2] a) T. Ohkuma, H. Ooka, S. Hashiguchi, T. Ikariya, R. Noyori, *J. Am. Chem. Soc.* **1995**, *117*, 2675–2676; b) H. Doucet, T. Ohkuma, K. Murata, T. Yokozawa, M. Kozawa, E. Katayama, A. F. England, T. Ikariya, R. Noyori, *Angew. Chem.* **1998**, *110*, 1792–1796; *Angew. Chem. Int. Ed.* **1998**, *37*, 1703–1707; c) T. Ohkuma, M. Koizumi, H. Doucet, T. Pham, M. Kozawa, K. Murata, E. Katayama, T. Yokozawa, T. Ikariya, R. Noyori, *J. Am. Chem. Soc.* **1998**, *120*, 13529–13530; d) K. Mikami, T. Korenaga, M. Terada, T. Ohkuma, T. Pham, R. Noyori, *Angew. Chem.* **1999**, *111*, 517–519; *Angew. Chem. Int. Ed.* **1999**, *38*, 495–497; for reviews see: e) R. Noyori, O. Ohkuma, *Angew. Chem.* **2001**, *113*, 40–75; *Angew. Chem. Int. Ed.* **2001**, *40*, 40–75; for mechanistic studies, see: f) 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; g) C. A. Sandoval, T. Ohkuma, K. Muñiz, R. Noyori, *J. Am. Chem. Soc.* **2003**, *125*, 13490–13503; h) T. Ohkuma, *Proc. Jpn. Acad. Ser. B* **2010**, *86*, 202–219.

[3] a) K. Mikami, T. Korenaga, M. Terada, T. Ohkuma, T. Pham, R. Noyori, *Angew. Chem.* **1999**, *111*, 517–519; *Angew. Chem. Int. Ed.* **1999**, *38*, 495–497; b) M. J. Burk, W. Hems, D. Herzberg, C. Malan, A. Zanotti-Gerosa, *Org. Lett.* **2000**, *2*, 4173–4176; c) J. Wu, J.-X. Ji, R. Guo, C.-H. Yeung, A. S. C. Chan, *Chem. Eur. J.* **2003**, *9*, 2963–2968; d) J.-H. Xie, L.-X. Wang, Y. Fu, S.-F. Zhu, B.-M. Fan, H.-F. Duan, Q.-L. Zhou, *J. Am. Chem. Soc.* **2003**, *125*, 4404–4405; e) C. Chen, R. A. Reamer, J. R. Chilenski, C. J. McWilliams, *Org. Lett.* **2003**, *5*, 5039–5042; f) A. Hu, H. L. Ngo, W. Lin, *Org. Lett.* **2004**, *6*, 2937–2940; g) W. Baratta, G. Chelucci, E. Herdtweck, S. Magnolia, K. Siega, P. Rigo, *Angew. Chem.* **2007**, *119*, 7795–7798; *Angew. Chem. Int. Ed.* **2007**, *46*, 7651–7654; h) H. Ooka, N. Arai, K. Azuma, N. Kurono, T. Ohkuma, *J. Org. Chem.* **2008**, *73*, 9084–9093; i) W. Li, X. Sun, L. Zhou, G. Hou, S. Yu, X. Zhang, *J. Org. Chem.* **2009**, *74*, 1397–1399; j) Y. Li, K. Ding, C. A. Sandoval, *Org. Lett.* **2009**, *11*, 907–910; k) Y. Li, Y. Zhou, Q. Shi, K. Ding, R. Noyori, C. A. Sandoval, *Adv. Synth. Catal.* **2011**, *353*, 495–500; l) K. Matsumura, N. Arai, K. Hori, T. Saito, N. Sayo, T. Ohkuma, *J. Am. Chem. Soc.* **2011**, *133*, 10696–10699; m) H. Guo, D. Liu, N. A. Butt, Y. Liu, W. Zhang, *Tetrahedron* **2012**, *68*, 3295–3299; n) A. Zirakzadeh, R. Schuecker, N. Gorgas, K. Mereiter, F. Spindler, W. Weissensteiner, *Organometallics* **2012**, *31*, 4241–4250.

[4] a) H. Zhang, T. Taketomi, T. Yoshizumi, H. Kumobayashi, S. Akutagawa, K. Mashima, H. Takaya, *J. Am. Chem. Soc.* **1993**, *115*, 3318–3319; b) T. Ohkuma, T. Hattori, H. Ooka, T. Inoue, R. Noyori, *Org. Lett.* **2004**, *6*, 2681–2683; c) N. Arai, M. Akashi, S. Sugizaki, H. Ooka, T. Inoue, T. Ohkuma, *Org. Lett.* **2010**, *12*, 3380–3383; d) T. Touge, T. Hakamata, H. Nara, T. Kobayashi, N. Sayo, T. Saito, Y. Kayaki, T. Ikariya, *J. Am. Chem. Soc.* **2011**, *133*, 14960–14963.

[5] T. Ohkuma, N. Utsumi, K. Tsutsumi, K. Murata, C. Sandoval, R. Noyori, *J. Am. Chem. Soc.* **2006**, *128*, 8724–8725.

[6] a) T. Ohkuma, M. Koizumi, K. Muñiz, G. Hilt, C. Kabuto, R. Noyori, *J. Am. Chem. Soc.* **2002**, *124*, 6508; b) T. Ohkuma, C. A. Sandoval, R. Srinivasan, Q. Lin, Y. Wei, K. Muñiz, R. Noyori, *J. Am. Chem. Soc.* **2005**, *127*, 8288–8289.

[7] K. Tsutsumi, T. Katayama, N. Utsumi, K. Murata, N. Arai, N. Kurono, T. Ohkuma, *Org. Process Res. Dev.* **2009**, *13*, 625–628.

[8] W. Tang, B. Qu, A. G. Capacci, S. Rodriguez, X. Wei, N. Haddad, B. Narayanan, S. Ma, N. Grinberg, N. K. Yee, D. Krishnamurthy, C. H. Senanayake, *Org. Lett.* **2010**, *12*, 176–179.

[9] See the Supporting Information for initial computational studies conducted to study the coordination of the diamines on the chiral Ru-BIBOP scaffold.

[10] W. Baratta, E. Herdtweck, K. Siega, M. Toniutti, P. Rigo, *Organometallics* **2005**, *24*, 1660–1669.

[11] T. Ohkuma, *Proc. Jpn. Acad. Ser. B* **2010**, *86*, 202–219.

[12] T. Ohkuma, M. Koizumi, M. Yoshida, R. Noyori, *Org. Lett.* **2010**, *12*, 1749–1751.

[13] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery Jr, J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, T. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J.

Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, D. J. Fox, *Gaussian 09*, Revision C.01, Gaussian, Inc., Wallingford CT, **2010**.

[14] a) T. H. Dunning Jr, P. J. Hay, in: *Modern Theoretical Chemistry*, (Ed.: H. F. Schaefer III), Vol. 3, Plenum, New York, **1976**, pp 1–28; b) P. J. Hay, W. R. Wadt, *J. Chem. Phys.* **1985**, *82*, 270–283; c) P. J. Hay, W. R. Wadt, *J. Chem. Phys.* **1985**, *82*, 299–310; d) W. R. Wadt, P. J. Hay, *J. Chem. Phys.* **1985**, *82*, 284–298.

[15] T. Touge, T. Hakamata, H. Nara, T. Kobayashi, N. Sayo, T. Saito, Y. Kayaki, T. Ikariya, *J. Am. Chem. Soc.* **2011**, *133*, 2299–2302.

