Asymmetric Catalysis

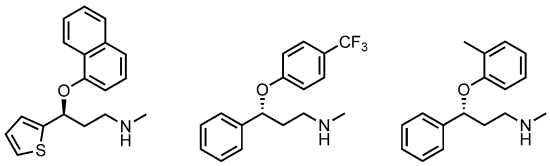
DOI: 10.1002/anie.201411384

$ZnCl_2$-Promoted Asymmetric Hydrogenation of β-Secondary-Amino Ketones Catalyzed by a P-Chiral Rh–Bisphosphine Complex**

*Qiupeng Hu, Zhenfeng Zhang, Yangang Liu, Tsuneo Imamoto, and Wanbin Zhang**

Abstract: *A new catalytic system has been developed for the asymmetric hydrogenation of β-secondary-amino ketones using a highly efficient P-chiral bisphosphine–rhodium complex in combination with $ZnCl_2$ as the activator of the catalyst. The chiral γ-secondary-amino alcohols were obtained in 90–94% yields, 90–99% enantioselectivities, and with high turnover numbers (up to 2000 S/C; S/C = substrate/catalyst ratio). A mechanism for the promoting effect of $ZnCl_2$ on the catalytic system has been proposed on the basis of NMR spectroscopy and HRMS studies. This method was successfully applied to the asymmetric syntheses of three important drugs, (S)-duloxetine, (R)-fluoxetine, and (R)-atomoxetine, in high yields and with excellent enantioselectivities.*

Over the last half century, remarkable progress has been made in the area of asymmetric hydrogenation and it remains an important topic of research because of its great potential for industrialization.[1,2] Among the many substrates, β-amino ketones have attracted considerable attention[3,4] because of their use in the preparation of chiral γ-amino alcohols, species widely used as ligands and pharmaceutical intermediates.[5,6] Unlike the extensive research on β-tertiary-amino ketones,[3] only a few studies have focused on the asymmetric hydrogenation of β-secondary-amino ketones for the preparation of chiral γ-secondary-amino alcohols.[3a,b,4] However, procedures involving β-secondary-amino ketones have higher efficiency and greater atom economy than those involving their tertiary counterparts in the syntheses of a number of important drugs such as (*S*)-duloxetine, (*R*)-fluoxetine, and (*R*)-atomoxetine (Figure 1).[6] A reason for the challenges facing the hydrogenation of β-secondary-amino ketones is probably due to the difficulty in finding an efficient catalyst system which has both high catalytic activity and stereoselectivity.



(*S*)-Duloxetine (*R*)-Fluoxetine (*R*)-Atomoxetine

Figure 1. Important drugs prepared from chiral γ-secondary-amino alcohols.

Over the last several years, our research has focused on the asymmetric hydrogenation of several types of substrates.[7] During our continuing research interest in the synthesis of the above-mentioned drug molecules, we have made encouraging progress towards the asymmetric hydrogenation of β-tertiary-amino ketones, a route through which (*R*)-fluoxetine and (*R*)-atomoxetine could be synthesized with excellent enantioselectivities.[7d] However, the application of this method to thienyl-substituted substrates was unsuccessful, probably due in part to the additional coordination ability of the sulfur atom. To realize the synthesis of (*S*)-duloxetine and improve the process efficiency, we have been searching for an efficient catalytic system for the asymmetric hydrogenation of β-secondary-amino ketones with both excellent enantioselectivity and high yield and turnover number.

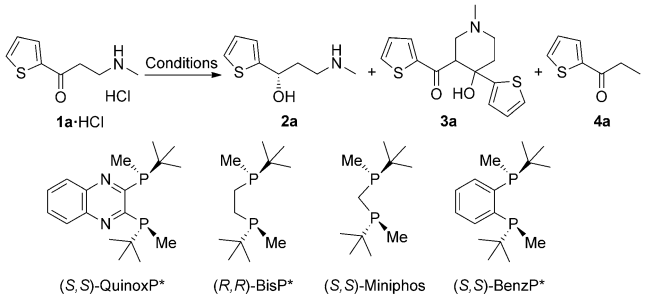
Electron-rich P-chiral bisphosphine ligands, including BisP*, Miniphos, QuinoxP*, and BenzP*, have been utilized since 1998 in the Rh-catalyzed asymmetric hydrogenation of enamides with remarkably high stereoselectivities and reactivities.[8] Considering their similar coordination configurations, these ligands were tested in the Rh-catalyzed asymmetric hydrogenation of β-methylamino ketones. Initially, 3-(methylamino)-1-(thiophen-2-yl)propan-1-one hydrochloride (**1a**·HCl) was used as a model substrate (Table 1). The hydrogen chloride is required to stabilize the free β-methylamino ketone. In the absence of hydrogen chloride, the free **1a** is unstable and can undergo a facile elimination to give an α,β-unsaturated ketone which subsequently undergoes a consecutive Michael addition and cyclization with **1a** to give compound **3a**. Hydrogenations involving the direct use of freshly prepared **1a** are also unsuccessful. However, the hydrogenation of **1a**·HCl also failed when performed under H_2 pressure (25 atm) and at room temperature. Only in the

[*] Q. Hu, Dr. Z. Zhang, Prof. Y. Liu, Prof. W. Zhang
School of Pharmacy, Shanghai Jiao Tong University
800 Dongchuan Road, Shanghai 200240 (P. R. China)
E-mail: wanbin@sjtu.edu.cn
Homepage: http://wanbin.sjtu.edu.cn
Prof. W. Zhang
School of Chemistry and Chemical Engineering
Shanghai Jiao Tong University
800 Dongchuan Road, Shanghai 200240 (P. R. China)
Prof. T. Imamoto
Department of Chemistry, Graduate School of Science
Chiba University, Chiba 263-8522 (Japan)

[**] This work was partially supported by the National Natural Science Foundation of China (No. 21172143, 21202096, 21232004, and 21472123), Science and Technology Commission of Shanghai Municipality (No. 14XD1402300), and Shanghai Jiao Tong University (SJTU). We gratefully acknowledge the generous gifts of the four P-chiral bisphosphine ligands from Nippon Chemical Industrial Co. Ltd. and Dr. Masashi Sugiya for helpful discussion. We also thank the Instrumental Analysis Center of SJTU for characterization.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201411384.

Table 1: Screening of ligands and optimization of reaction conditions.[a]



Entry	Ligand (S/C)	Base	Additive (equiv)	Yield of **2a** (**3a**/**4a**) [%][b]	*ee* of **2a** [%][c]
1	QuinoxP* (200)	K_2CO_3	None	24 (24/6)	93
2	BenzP* (200)	K_2CO_3	None	51 (5/14)	98
3	BisP* (200)	K_2CO_3	None	20 (30/0)	n.d.
4	Miniphos (200)	K_2CO_3	None	9 (55/18)	n.d.
5	BenzP* (200)	Cs_2CO_3	None	95 (0/2)	98
6	BenzP* (500)	Cs_2CO_3	None	67 (13/7)	98
7	BenzP* (500)	Cs_2CO_3	$ZnCl_2$ (1.0)	98 (0/2)	99
8	BenzP* (500)	Cs_2CO_3	$ZnCl_2$ (0.8)	97 (0/2)	99
9	BenzP* (500)	Cs_2CO_3	$ZnCl_2$ (0.6)	97 (0/3)	99
10	BenzP* (500)	Cs_2CO_3	$ZnCl_2$ (0.4)	97 (0/3)	99
11	BenzP* (500)	Cs_2CO_3	$ZnCl_2$ (0.2)	76 (4/0)	98
12	BenzP* (1000)	Cs_2CO_3	$ZnCl_2$ (0.4)	96 (0/4)	99
13	BenzP* (2000)	Cs_2CO_3	$ZnCl_2$ (0.4)	65 (13/3)	99
14[d]	BenzP* (2000)	Cs_2CO_3	$ZnCl_2$ (0.4)	89 (1/6)	99

[a] Conditions: **1a**·HCl (0.2 M), [Rh(ligand)(cod)]SbF_6, base (0.5 equiv), $ZnCl_2$, MeOH, H_2 (25 atm), RT, 20 h. [b] The yields were calculated from ^{1}H NMR spectra. [c] The *ee* values were determined after acetylation by HPLC using chiral columns. [d] 48 h. S/C = substrate/catalyst ratio. cod = 1,5-cyclooctadiene. n.d. = not determined.

presence of a base, such as K_2CO_3, could product **2a** be obtained in measurable yields. Initial screening of ligands (Table 1, entries 1–4), using K_2CO_3 as a base and with a substrate/catalyst ratio of 200, showed that [Rh((*S*,*S*)-BenzP*)(cod)]SbF_6 was the most efficient catalyst affording **2a** with excellent enantioselectivity (98%) but with a moderate yield of 51% (entry 4). In this case, a considerable amount of by-products **3a** (5%) and **4a** (14%) were formed, of which **4a** is produced from the hydrogenation of the above-mentioned α,β-unsaturated ketone. Based on these results, it can be concluded that: a) before hydrogenation, the hydrogen chloride plays as an essential part in protecting the amino group and thus stabilizing the substrate, and b) during hydrogenation, a base is required to neutralize the hydrogen chloride to release the amino group and activate the substrate. Therefore, if the rate of hydrogenation of **1a** is too slow, large quantities of **3a** and **4a** will be produced resulting in a low yield of **2a**. To increase the yield of the desired product **2a**, the rate of hydrogenation must be increased: this is the fundamental challenge in developing an efficient catalyst and searching for optimized catalytic conditions.

First, different solvents and bases were screened using [Rh((*S*,*S*)-BenzP*)(cod)]SbF_6 as a catalyst (see Table S1 in the Supporting Information for details). MeOH and Cs_2CO_3 proved to be the best solvent and base, respectively, for the reaction, affording the desired product **2a** with not only an excellent enantioselectivity of 98% but also the highest yield of 95% (Table 1, entry 5). To evaluate the activity of the catalytic system, we carried out the hydrogenation at a higher S/C ratio (500) using [Rh((*S*,*S*)-BenzP*)(cod)]SbF_6 as the catalyst and Cs_2CO_3 as the base in MeOH. However, the yield of **2a** decreased from 95% to 67% and significant amounts of by-products were generated (entries 6 versus 5). No further improvement was achieved by altering the H_2 pressure and reaction temperature. A possible reason for the low turnover number may be due to the deactivation of the catalyst caused by the accumulation of a less active species, such as a chloride-bridged trinuclear rhodium complex.[9] We envisaged that this problem could be solved by competitive coordination, that is, by introducing another metal which has a higher affinity for the chloride ion than the rhodium atom and can therefore extract the chloride. This will allow for the catalyst to be reactivated. Thus, we investigated the effect of a number of metal salts as additives for the reaction (see Table S1 for details). To our delight, when $ZnCl_2$ (1.0 equiv) was added to the reaction mixture, the yield increased to 98% with an accompanying increase of *ee* to 99% (Table 1, entry 7). The reaction still completed smoothly when the loading of $ZnCl_2$ was decreased from 1.0 equivalent to 0.4 equivalents (entries 7–10). Further decreasing the loading amount to 0.2 equivalents of $ZnCl_2$ lowered both the yield and *ee* value (entry 11). Increasing the S/C ratio to 1000 also gave a similarly good result in the presence of 0.4 equivalents of $ZnCl_2$ (entry 12). The hydrogenation gave the desired product in 65% yield and 99% *ee* even at S/C = 2000 (entry 13). Further extending the reaction time to 48 hours increased the yield to 89% with 99% *ee* (entry 14).

To uncover more evidence for the competitive coordination, the catalyst system was studied using ^{31}P NMR spectroscopy (Figure 2) and HRMS (Figures S1 and S2). The catalyst precursor [Rh((*S*,*S*)-BenzP*)(cod)]SbF_6 was

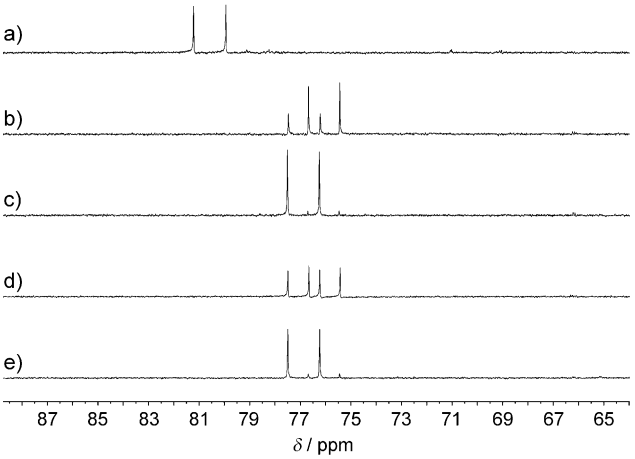
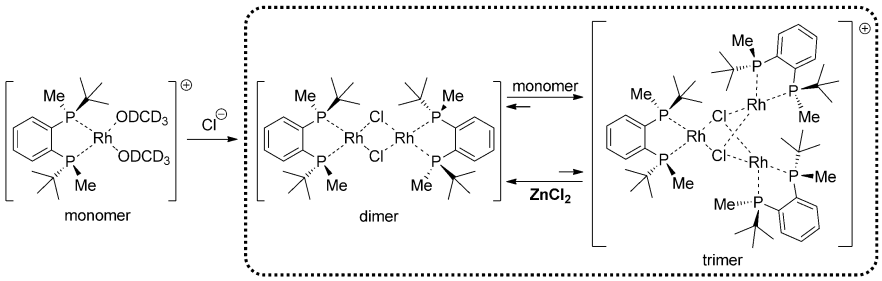


Figure 2. ^{31}P NMR spectroscopic studies on the catalyst system. Spectra of the complex [Rh((*S*,*S*)-BenzP*)$(CD_3OD)_2$]SbF_6 a) before and b) after hydrogenation for 30 min under H_2 (25 atm) at room temperature and c) after subsequent addition of $ZnCl_2$. Spectra of [Rh((*S*,*S*)-BenzP*)$(CD_3OD)_2$]SbF_6 d) after addition of CsCl and e) after subsequent addition of $ZnCl_2$.



Scheme 1. Proposed mechanism for the promoting effect of $ZnCl_2$ on the activity of the rhodium complex in the asymmetric hydrogenation reaction.

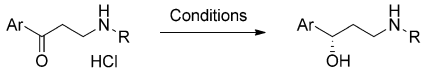
smoothly converted into the solvent-coordinated complex $[Rh((S,S)\text{-BenzP*})(CD_3OD)_2]^+$ (monomer structure in Scheme 1; two signals at $\delta = 81.2$ and 79.9 ppm in Figure 2a).[8d] This solvent-coordinated complex was then added to an autoclave which contained **1a**·HCl (4.0 equiv) and Cs_2CO_3 (2.0 equiv) in CD_3OD. After hydrogenation for 30 minutes under 25 atm of H_2 at room temperature, the resonance signals in the ^{31}P NMR spectrum of the solvent-coordinated complex $[Rh((S,S)\text{-BenzP*})(CD_3OD)_2]^+$ disappeared and two pairs of new signals appeared (major signals appeared at $\delta = 76.7$ and 75.4 ppm, with minor signals at $\delta =$ 77.5 and 76.2 ppm in Figure 2b). The major resonance signals can be attributed to the chloride-bridged trinuclear rhodium complex (trimer in Scheme 1) which is more stable and has lower catalytic activity.[9] This trimer was confirmed by examination of HRMS spectra in which a signal at *m*/*z* 1225.1090 and its corresponding isotopic peaks are attributed to the complex $[Rh_3(\mu_3\text{-}Cl)_2(BenzP^*)_3]^+$ (Figure S1). The two minor signals are considered to be due to the chloride-bridged binuclear rhodium complex (dimer in Scheme 1), which is less stable and has a higher catalytic activity.[10] When $ZnCl_2$ was added to the above solution, the signals attributable to the trimer almost vanished and the intensity of the signals corresponding to the dimer increased (Figure 2c). In the HRMS spectra (Figure S2), signals attributable to the dimer as $[Rh_2(\mu_2\text{-}Cl)_2(BenzP^*)_2]^+$ at *m*/*z* 840.0657 and its isotopic peaks and the signal for the monomer as $[Rh(BenzP^*)]^+$ at *m*/*z* 385.0622 were detected. The trimer and dimer were also formed when CsCl was directly added to a solution of $[Rh((S,S)\text{-BenzP*})(CD_3OD)_2]SbF_6$ (Figure 2d). Similarly, the addition of $ZnCl_2$ to the above solution led to the conversion of the trimer into the dimer as evidenced by the ^{31}P NMR spectra (Figure 2e).

From the above results, a mechanism for the promoting effect of $ZnCl_2$ is proposed in Scheme 1. First, the cationic solvated monomer is converted into the trimer and dimer in the presence of Cl^- ions. The trimer is the major species in the equilibrium between the trimer/Cl^- and dimer because of its greater stability. The added $ZnCl_2$ then competitively coordinates to the chloride ion[11] and converts the less-active chloride-bridged trinuclear rhodium complex (trimer) into a chloride-bridged binuclear rhodium complex (dimer). The dimer is less stable and more reactive and is directly converted into a solvated Rh^I monomer or a Rh^{III} monomer by the oxidative addition of hydrogen.[10] In doing so, the rhodium catalyst is reactivated to provide a higher turnover number.

A similar promoting effect using $ZnCl_2$ was also found in the asymmetric hydrogenation of the hydrochloride salt of an α-secondary-amino ketone to its corresponding β-secondary-amino alcohol. As expected, both the yield and *ee* value of the hydrogenation increased after the addition of $ZnCl_2$ (see the Supporting Information for details).

With the optimized reaction conditions in hand, we extended the substrate scope of the hydrogenation reaction using a catalyst loading of 0.2 mol%, that is with a S/C ratio of 500 (Table 2). Changing the R group of the amine from Me to Et and Bn (benzyl) did not significantly affect reactivity and enantioselectivity (entries 1–3). A substrate with a heterocyclic 2-furyl group could also be successfully hydrogenated to give the desired product in 92% yield with 99% *ee* (entry 4). Other substrates with substituted aryl groups could also be successfully hydrogenated in high yields and with excellent enantioselectivities (entry 5–20). A phenyl-substituted substrate afforded a product with a slightly lower enantioselectivity (entry 5), whereas aryl groups with 4-substituted electron-withdrawing F, Cl, or Br substituents (entries 6–8) and electron-donating Me or MeO substituents (entries 10

Table 2: BenzP*–Rh catalyzed asymmetric hydrogenation of various β-secondary-amino ketones.[a]



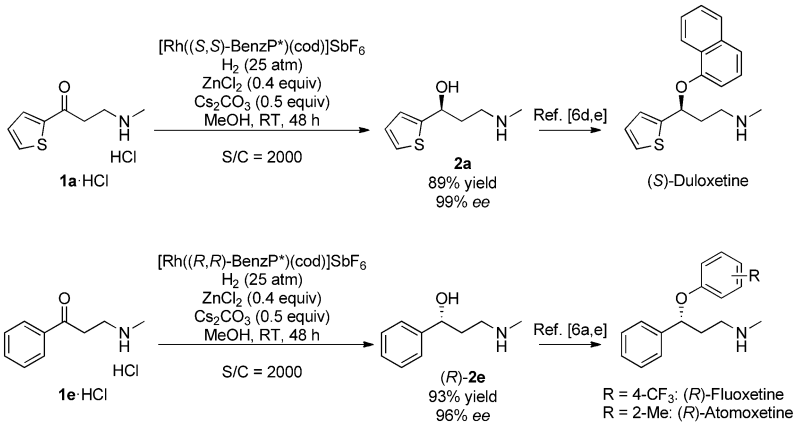
1·HCl **2**

Entry	**1**	Ar	R	Yield [%][b]	*ee* [%][c]
1	**a**	2-thienyl	Me	94	99
2	**b**	2-thienyl	Et	90	99
3	**c**	2-thienyl	Bn	92	97
4	**d**	2-furyl	Me	92	99
5	**e**	C_6H_5	Me	92	95
6	**f**	$4\text{-}FC_6H_4$	Me	93	99
7	**g**	$4\text{-}ClC_6H_4$	Me	91	99
8	**h**	$4\text{-}BrC_6H_4$	Me	92	99
9	**i**	$4\text{-}CF_3C_6H_4$	Me	91	94
10	**j**	$4\text{-}MeC_6H_4$	Me	94	99
11	**k**	$3\text{-}MeC_6H_4$	Me	92	99
12	**l**	$2\text{-}MeC_6H_4$	Me	93	98
13	**m**	$4\text{-}MeOC_6H_4$	Me	92	99
14	**n**	$3\text{-}MeOC_6H_4$	Me	92	98
15	**o**	$2\text{-}MeOC_6H_4$	Me	90	93
16	**p**	$3,4\text{-}(MeO)_2C_6H_3$	Me	94	99
17	**q**	$2,4\text{-}(MeO)_2C_6H_3$	Me	90	90
18	**r**	2-naphthyl	Me	92	99
19	**s**	1-naphthyl	Me	90	95
20	**t**	3,4-(methylenedioxy)C_6H_3	Me	94	99

[a] Conditions: **1**·HCl (1.0 mmol), $[Rh((S,S)\text{-BenzP*})(cod)]SbF_6$ (0.2 mol%), Cs_2CO_3 (0.5 equiv), $ZnCl_2$ (0.4 equiv), MeOH (5 mL), H_2 (25 atm), RT, 20 h. [b] Yield of isolated product. [c] The *ee* values were determined after acetylation by HPLC using chiral columns.

and 13) could all be reduced with 99% *ee*. A substrate with a more electron-deficient aryl group (CF_3-substituted) was reduced with a lower enantioselectivity of 94% *ee* (entry 9). Substrates with substituents located at different positions on the aryl ring were reduced with varying *ee* values. Higher enantioselectivities were achieved for substrates having aryl rings substituted at the 4- and 3-positions, whereas those with groups substituted at the 2-position were reduced with slightly lower enantioselectivities (entries 10–15). A similar substituent effect can also be seen between substrates substituted with 3,4-$(MeO)_2C_6H_3$ and 2,4-$(MeO)_2C_6H_3$ groups (entries 16 and 17), and 2-naphthyl- and 1-naphthyl-substituted substrates (entries 18 and 19). Finally, a substrate having a less sterically hindered substituent, specifically a 3,4-methylenedioxy group on the aryl ring, could be reduced with excellent enantioselectivity (entry 20).

The developed method was successfully applied to the synthesis of three important chiral pharmaceuticals (Scheme 2). (*S*)-3-(methylamino)-1-(thiophen-2-yl)propan-1-ol ((*S*)-**2a**) and (*R*)-3-(methylamino)-1-phenylpropan-1-ol



Scheme 2. Application of the $ZnCl_2$-promoted bisphosphine–rhodium catalytic system for the syntheses of three important chiral pharmaceuticals.

((*R*)-**2e**) were prepared in high yields and with excellent enantioselectivities using our catalytic system with an S/C of 2000. These intermediates can be easily etherified using reported methods[6a,d,e] to give (*S*)-duloxetine, (*R*)-fluoxetine, and (*R*)-atomoxetine with retention of configurations.

In conclusion, we have developed an efficient catalytic system using a P-chiral bisphosphine–rhodium complex and $ZnCl_2$ as a catalyst activator for the asymmetric hydrogenation of β-secondary-amino ketones. The chiral γ-secondary-amino alcohols were obtained in high yields (90–94%), with excellent enantioselectivities (90–99%), and with high turnover numbers (up to 2000 S/C). On the basis of HRMS and NMR spectroscopic studies, a mechanism for the promoting effect of $ZnCl_2$ on the catalytic system is proposed. Furthermore, the chiral pharmaceutical drugs (*R*)-atomoxetine, (*R*)-fluoxetine, and (*S*)-duloxetine have been successfully prepared with excellent yields and *ee* values and with retention of configuration by application of this method. It is believed that the concept of competitive coordination to reactivate the transition-metal catalyst can be applied to other related catalytic transformations.

Experimental Section

General procedure for asymmetric hydrogenation: Compound **1**·HCl (1.0 mmol), Rh[(*S*,*S*)-BenzP*)(cod)]SbF_6 (0.002 mmol), Cs_2CO_3 (0.5 mmol), and $ZnCl_2$ (0.4 mmol) were added to an autoclave flask and the system was evacuated and filled with hydrogen. After repeating this operation three times, degassed methanol (5 mL) was added and the hydrogen pressure was adjusted to 25 atm. After vigorous stirring at room temperature for 20 h, the reaction mixture was evaporated under reduced pressure. The conversion of substrate into product was calculated from the ^1H NMR spectrum of the crude product. The residue was passed through a short column of basic Al_2O_3 using CH_2Cl_2/MeOH (30:1 v/v) as the eluent to give product **2**. The *ee* was determined after acetylation by HPLC using chiral columns.

Received: November 24, 2014
Published online: ■■ ■■, ■■■■

Keywords: amino alcohols · asymmetric catalysis · hydrogen · P ligands · rhodium

[1] For representative reviews, see: a) *Handbook of Homogeneous Hydrogenation* (Eds.: J. G. de Vries, C. J. Elsevier), Wiley-VCH, Weinheim, **2007**; b) *Phosphorus Ligands in Asymmetric Catalysis* (Ed.: A. Börner), Wiley-VCH, Weinheim, **2008**; c) *Asymmetric Catalysis on Industrial Scale*, 2nd ed. (Eds.: H.-U. Blaser, H.-J. Federsel), Wiley-VCH, Weinheim, **2010**.

[2] For recent representative examples, see: a) S. Song, S.-F. Zhu, Y.-B. Yu, Q.-L. Zhou, *Angew. Chem. Int. Ed.* **2013**, *52*, 1556–1559; *Angew. Chem.* **2013**, *125*, 1596–1599; b) S. Song, S.-F. Zhu, L.-Y. Pu, Q.-L. Zhou, *Angew. Chem. Int. Ed.* **2013**, *52*, 6072–6075; *Angew. Chem.* **2013**, *125*, 6188–6191; c) K. Dong, Y. Li, Z. Wang, K. Ding, *Angew. Chem. Int. Ed.* **2013**, *52*, 14191–14195; *Angew. Chem.* **2013**, *125*, 14441–14445; d) X. Liu, Z. Han, Z. Wang, K. Ding, *Angew. Chem. Int. Ed.* **2014**, *53*, 1978–1982; *Angew. Chem.* **2014**, *126*, 2009–2013; e) Z. Zhang, H. Du, *Angew. Chem. Int. Ed.* **2014**, DOI: 10.1002/anie.201409471; *Angew. Chem.* **2014**, DOI: 10.1002/ange.201409471; f) P. A. Dub, N. J. Henson, R. L. Martin, J. C. Gordon, *J. Am. Chem. Soc.* **2014**, *136*, 3505–3521; g) Y. Li, S. Yu, X. Wu, J. Xiao, W. Shen, Z. Dong, J. Gao, *J. Am. Chem. Soc.* **2014**, *136*, 4031–4039; h) Q. Wang, W. Huang, H. Yuan, Q. Cai, L. Chen, H. Lv, X. Zhang, *J. Am. Chem. Soc.* **2014**, *136*, 16120–16123; i) B. K. Peters, T. Zhou, J. Rujirawanich, A. Cadu, T. Singh, W. Rabten, S. Kerdphon, P. G. Andersson, *J. Am. Chem. Soc.* **2014**, *136*, 16557–16562.

[3] a) S. Sakuraba, K. Achiwa, *Synlett* **1991**, 689–690; b) S. Sakuraba, K. Achiwa, *Chem. Pharm. Bull.* **1995**, *43*, 748–753; c) T. Ohkuma, D. Ishii, H. Takeno, R. Noyori, *J. Am. Chem. Soc.* **2000**, *122*, 6510–6511; d) T. Ohkuma, M. Koizumi, M. Yoshida, R. Noyori, *Org. Lett.* **2000**, *2*, 1749–1751; e) T. Ohkuma, M. Koizumi, K. Muñiz, G. Hilt, C. Kabuto, R. Noyori, *J. Am. Chem. Soc.* **2002**, *124*, 6508–6509; f) D. G. Genov, D. J. Ager, *Angew. Chem. Int. Ed.* **2004**, *43*, 2816–2819; *Angew. Chem.* **2004**, *116*, 2876–2879; g) Q. Zhu, D. Shi, C. Xia, H. Huang, *Chem. Eur. J.* **2011**, *17*, 7760–7763.

[4] D. Liu, W. Gao, C. Wang, X. Zhang, *Angew. Chem. Int. Ed.* **2005**, *44*, 1687 – 1689; *Angew. Chem.* **2005**, *117*, 1715 – 1717.

[5] a) M. Panda, P.-W. Phuan, M. C. Kozlowski, *J. Org. Chem.* **2003**, *68*, 564 – 571; b) Y. Hari, T. Aoyama, *Synthesis* **2005**, 583 – 587; c) C.-L. Liu, C.-Y. Wei, S.-W. Wang, Y.-G. Peng, *Chirality* **2011**, *23*, 921 – 928.

[6] a) Y. Gao, K. B. Sharpless, *J. Org. Chem.* **1988**, *53*, 4081 – 4084; b) H. Kakei, T. Nemoto, T. Ohshima, M. Shibasaki, *Angew. Chem. Int. Ed.* **2004**, *43*, 317 – 320; *Angew. Chem.* **2004**, *116*, 321 – 324; c) Y. Fujima, M. Ikunaka, T. Inoue, J. Matsumoto, *Org. Process Res. Dev.* **2006**, *10*, 905 – 913; d) A. Träff, R. Lihammar, J. Bäckvall, *J. Org. Chem.* **2011**, *76*, 3917 – 3921; e) J.-N. Zhou, Q. Fang, Y.-H. Hu, L.-Y. Yang, F.-F. Wu, L.-J. Xie, J. Wu, S. Li, *Org. Biomol. Chem.* **2014**, *12*, 1009 – 1017.

[7] For representative examples, see: a) F. Tian, D. Yao, Y. Liu, F. Xie, W. Zhang, *Adv. Synth. Catal.* **2010**, *352*, 1841 – 1845; b) Y. Liu, W. Zhang, *Angew. Chem. Int. Ed.* **2013**, *52*, 2203 – 2206; *Angew. Chem.* **2013**, *125*, 2259 – 2262; c) J. Chen, D. Liu, N. Butt, C. Li, D. Fan, Y. Liu, W. Zhang, *Angew. Chem. Int. Ed.* **2013**, *52*, 11632 – 11636; *Angew. Chem.* **2013**, *125*, 11846 – 11850; d) J. Wang, D. Liu, Y. Liu, W. Zhang, *Org. Biomol. Chem.* **2013**, *11*, 3855 – 3861; e) Y. Liu, I. D. Gridnev, W. Zhang, *Angew. Chem. Int. Ed.* **2014**, *53*, 1901 – 1905; *Angew. Chem.* **2014**, *126*, 1932 – 1936.

[8] a) T. Imamoto, J. Watanabe, Y. Wada, H. Masuda, H. Yamada, H. Tsuruta, S. Matsukawa, K. Yamaguchi, *J. Am. Chem. Soc.* **1998**, *120*, 1635 – 1636; b) Y. Yamanoi, T. Imamoto, *J. Org. Chem.* **1999**, *64*, 2988 – 2989; c) T. Imamoto, K. Sugita, K. Yoshida, *J. Am. Chem. Soc.* **2005**, *127*, 11934 – 11935; d) T. Imamoto, K. Tamura, Z. Zhang, Y. Horiuchi, M. Sugiya, K. Yoshida, A. Yanagisawa, I. D. Gridnev, *J. Am. Chem. Soc.* **2012**, *134*, 1754 – 1769.

[9] a) A. Preetz, W. Baumann, H.-J. Drexler, C. Fischer, J. Sun, A. Spannenberg, O. Zimmer, W. Hell, D. Heller, *Chem. Asian J.* **2008**, *3*, 1979 – 1982; b) A. Preetz, H.-J. Drexler, C. Fischer, Z. Dai, A. Börner, W. Baumann, A. Spannenberg, R. Thede, D. Heller, *Chem. Eur. J.* **2008**, *14*, 1445 – 1451; c) C. Fischer, C. Kohrt, H.-J. Drexler, W. Baumann, D. Heller, *Dalton Trans.* **2011**, *40*, 4162 – 4166; d) A. Preetz, C. Kohrt, A. Meißner, S. Wei, H.-J. Drexler, H. Buschmann, D. Heller, *Catal. Sci. Technol.* **2013**, *3*, 462 – 468; e) A. Meißner, E. Alberico, H.-J. Drexler, W. Baumann, D. Heller, *Catal. Sci. Technol.* **2014**, *4*, 3409 – 3425; f) A. Meißner, A. König, H.-J. Drexler, R. Thede, W. Baumann, D. Heller, *Chem. Eur. J.* **2014**, *20*, 14721 – 14728.

[10] a) P. Krüger, H. Werner, *Eur. J. Inorg. Chem.* **2004**, 481 – 491; b) S. A. Colebrooke, S. B. Duckett, J. A. B. Lohman, R. Eisenberg, *Chem. Eur. J.* **2004**, *10*, 2459 – 2474.

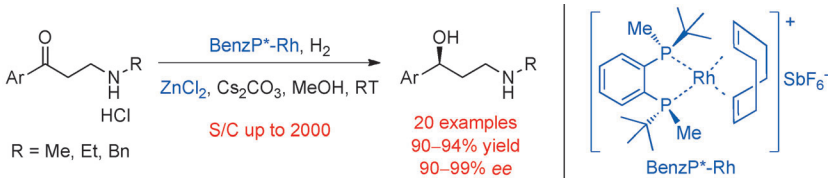
[11] a) O. P. Gladkikh, N. F. Curtis, S. L. Heath, *Acta Crystallogr. Sect. C* **1997**, *53*, 197 – 200; b) P. Kofod, P. Harris, *Inorg. Chem.* **2004**, *43*, 2680 – 2688; c) J.-i. Ito, S. Ujiie, H. Nishiyama, *Organometallics* **2009**, *28*, 630 – 638.

Communications

Asymmetric Catalysis

Q. Hu, Z. Zhang, Y. Liu, T. Imamoto, W. Zhang* ——— ■■■■–■■■■

$ZnCl_2$-Promoted Asymmetric Hydrogenation of β-Secondary-Amino Ketones Catalyzed by a P-Chiral Rh–Bisphosphine Complex



Competitive coordination: Chiral γ-secondary-amino alcohols were obtained in high yields and with excellent enantioselectivities by hydrogenation of β-secondary-amino ketones. NMR spectroscopy and HRMS are used to investigate the mechanism for the activation effect of $ZnCl_2$ on the bisphosphine–rhodium catalyst.

