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Short communication

Ruthenium-catalyzed hydrogenation of aromatic ketones using chiral diamine and monodentate achiral phosphine ligands

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ABSTRACT

The Ru-catalyzed asymmetric hydrogenation of ketones with chiral diamine and monodentate achiral phosphine has been developed. A wide range of ketones were hydrogenated to afford the corresponding chiral secondary alcohols in good to excellent enantioselectivities (up to 98.1% ee). In addition, an appropriate mechanism for the asymmetric hydrogenation was proposed and verified by NMR spectroscopy.

1. Introduction

Enantiomerically pure alcohols, especially those bearing heterocycles, are important building blocks and key intermediates for the production of biologically active molecules and chiral auxiliaries such as medicines, perfumes, and agrochemicals [1,2]. Undoubtedly, from the view of green chemistry, asymmetric hydrogenation of prochiral ketones represents a convenient approach towards enantiomerically enriched alcohols in view of its atom economy, easy handling, high activity, low catalyst loading and low cost of reducing agents on both laboratory and industrial scales [3,4]. Based on the researches of Noyori and co-workers [5,6], chiral diphosphine/diamine/transition metal complexes were investigated to balance conversion, selectivity and atom efficiency of asymmetric reduction of carbonyl compounds. Ru-BICP-chiral-diamine-KOH and TunePhos/diamine-Ru(II) complex/*t*-BuOK have been disclosed and proved to be efficient in the enantioselective hydrogenation of aromatic ketones [7,8]. In 2000, Zanotti-Gerosa and coworkers reported PhanePhos-ruthenium-diamine complexes and various aromatic, heteroaromatic and α, β-unsaturated ketones were effectively hydrogenated [9]. Chen et al. demonstrated asymmetric hydrogenation of aromatic-heteroaromatic ketone using trans-$RuCl_2$[(*R*)-xylbinap][(*R*)-daipen] as a catalyst afforded secondary alcohol with 99.4% ee [10]. Zhou and co-workers developed spiro diphosphines that are highly efficient for the asymmetric hydrogenation of ketones [11,12]. Moreover, a great deal of chiral compounds such as NN [13], NNN [14], SN [15], NO [16], PN [17,18], PNO [19], PNNP [20,21], ferrocene-based ligands [22,23], macrocyclic ligands [24], hemisalen type ligands [25] have been designed, synthesized and applied successfully in asymmetric hydrogenation. As it can be seen, the high enantioselectivity was imparted by the synergistic effect of the chiral ligands, which are often expensive owing to difficulties in complex structures constructed using multi-step reactions. In addition, it is noteworthy that a variety of reactions still lack effective chiral ligands and the enantioselectivities in many reactions are substrate dependent [26]. Therefore, there is a continuing interest in the development of simple, less expensive and more efficient catalysts for the asymmetric hydrogenation of carbonyl compounds under mild conditions to access chiral alcohols. Recently, we have reported the effective catalytic performances of iridium combining with chiral diamine and achiral phosphine in the asymmetric hydrogenation of aryl, heteroaryl ketones and enones [27–29]. Herein we reported a simple ruthenium complex coordinated with *o*-MOTPP and chiral diamine as well as their activities explored as catalysts for the asymmetric hydrogenation of simple aromatic and heteroaromatic ketones.

2. Experimental part

2.1. General information

All reagents were commercially available or prepared according to

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published procedures. The purity of hydrogen was over 99.99%. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker NMR 400 MHz spectrometer. The conversions and ee values were determined by GC-9790 using a chiral capillary column (β-DEX^{120} column, 25 m × 0.25 mm). Optical rotations were taken on an IP-Digi 300 polarimeter.

2.2. Typical procedure for asymmetric hydrogenation of ketones

Ruthenium precursor, ligands, solvent, base and ketones were added to a 50 mL stainless autoclave with a magnetic stirrer. The autoclave is then charged H_2. After stirring for 2 h, the conversions and enantioselectivity values were analyzed by GC. The ee values of chiral alcohols were calculated from the equations enantioselectivity values (ee, %) = |R - S| / |R + S|.

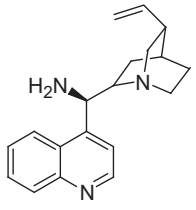
3. Results and discussion

Our investigation was started with the asymmetric hydrogenation of acetophenone as a model reaction. Initially, the activity of different ruthenium precursors was evaluated in the presence of chiral diamine **1** and *o*-MOTPP. Most ruthenium precursors gave only low conversion. Notably, benzylidene-bis(tricyclohexylphosphine)dichlororuthenium showed 42.3% conversion and 90.2% ee. Since the steric and electronic properties of ligands are two critical factors for the asymmetric hydrogenation [30,31], simple and commercially available monodentate phosphine with different electronic and steric properties were investigated in the model reaction. As shown in Table 1, lower conversion and enantioselectivity were obtained separately with phosphine or diamine added alone (Table 1, entry 1–2). As expected, both triphenylphosphine and 9-amino(9-deoxy) epi-cinchonine were used as ligands, the enantioselectivities increased dramatically (Table 1, entry 3). Furthermore, more hindered triarylphosphine-bearing substituents on the benzene ring, such as MOTPP, MTPP and TFTPP, were evaluated, demonstrating higher efficiency than triphenylphosphine in asymmetric hydrogenation (Table 1, entry 4–8). A more pronounced steric effect on the catalytic efficiency was observed with *o*-MOTPP used, giving 1-phenylethanol in excellent 90.2% ee value (Table 1, entry 4). These results indicate that the sterically hindered monophosphines are effective for the asymmetric hydrogenation of acetophenone. Next, a survey of chiral diamines derived from cinchona alkaloid indicated that 9-amino(9-deoxy) epi-cinchonine was better choice with respect to higher conversions and enantioselectivities (Table 1, entries 4, 9–12).

To improve these results further, different molar ratios were tested. The better molar ratios of chiral diamine **1**/*o*-MOTPP/ruthenium was 2/1/1. Additionally, the optimization studies exhibited that good catalytic activity was gained with 1-PrOH and LiOH.

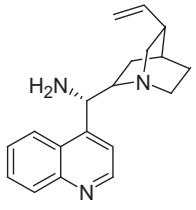
With standard conditions realized, we next extended the catalytic system to involve asymmetric hydrogenation of substituted acetophenone and heteroaromatic ketones. As seen from Scheme 1, the substrates bearing different *ortho* substitution patterns (F-, Cl-, Br-, CF_3, CH_3-, OCH_3-) at the phenyl group were hydrogenated smoothly in high enantioselectivities (90.5–98.1% ee), regardless of their electronic

Table 1
The effect of chiral diamines and achiral phosphines for asymmetric hydrogenation of ketones[a].



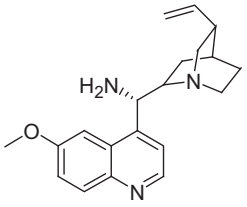
1

9-Amino(9-deoxy)epi-cinchonine



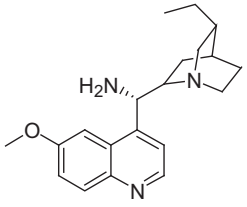
2

9-Amino(9-deoxy)epi-cinchonidine



3

9-Amino-(9-deoxy)epi-quinine



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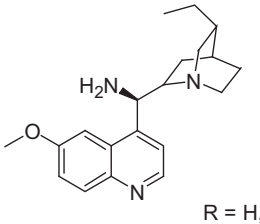
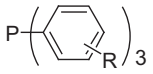
9-Amino-(9-deoxy)epi-dihydroquinine



5

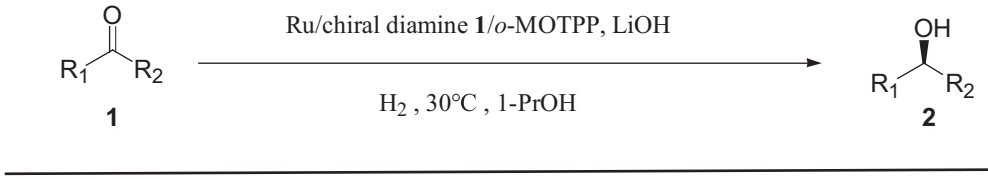
9-Amino-(9-deoxy)epi-dihydroquinidine

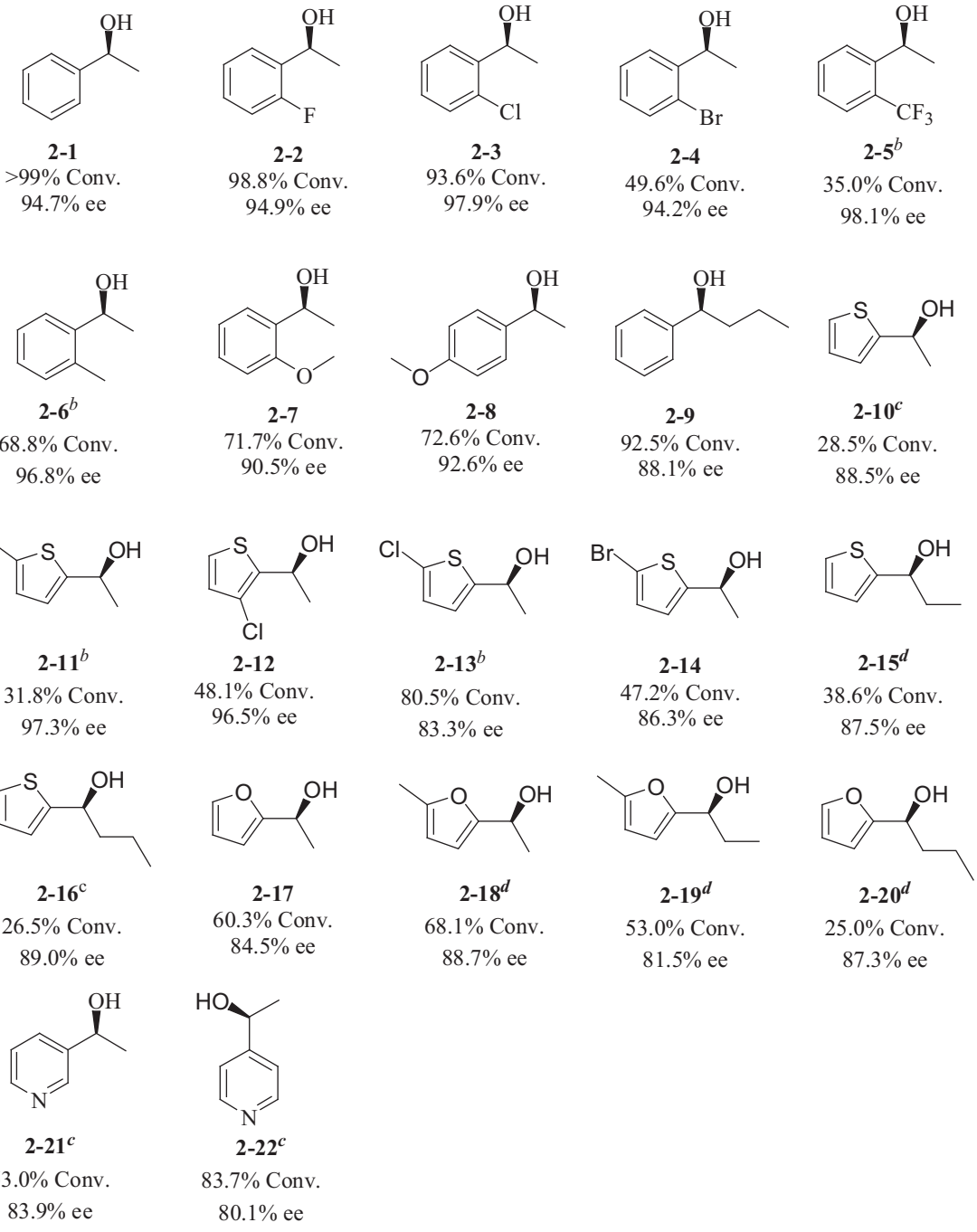


R = H, *o*-OCH_3, *m*-OCH_3, *p*-OCH_3, *p*-CH_3, *p*-CF_3

Entry	Chiral diamine	Achiral phosphine	Con(%)	Ee(%)	Config.
1	1	–	<3	–	–
2	–	*o*-MOTPP	<3	–	–
3	1	TPP	4.1	70.4	S
4	1	*o*-MOTPP	42.3	90.2	S
5	1	*m*-MOTPP	18.7	79.7	S
6	1	*p*-MOTPP	8.9	75.6	S
7	1	*p*-MTPP	26.0	77.7	S
8	1	*p*-TFTPP	12,4	85.3	S
9	2	*o*-MOTPP	13.5	57.8	R
10	3	*o*-MOTPP	33.7	84.2	R
11	4	*o*-MOTPP	18.1	51.0	R
12	5	*o*-MOTPP	38.3	56.5	S

[a] Substrate/Ru/chiral diamine/achiral phosphine = 400/1/1/2, acetophenone: 0.857 mol/L, LiOH: 0.1 mol/L, EtOH: 2 ml, 25 °C, 6 MPa, 2 h.



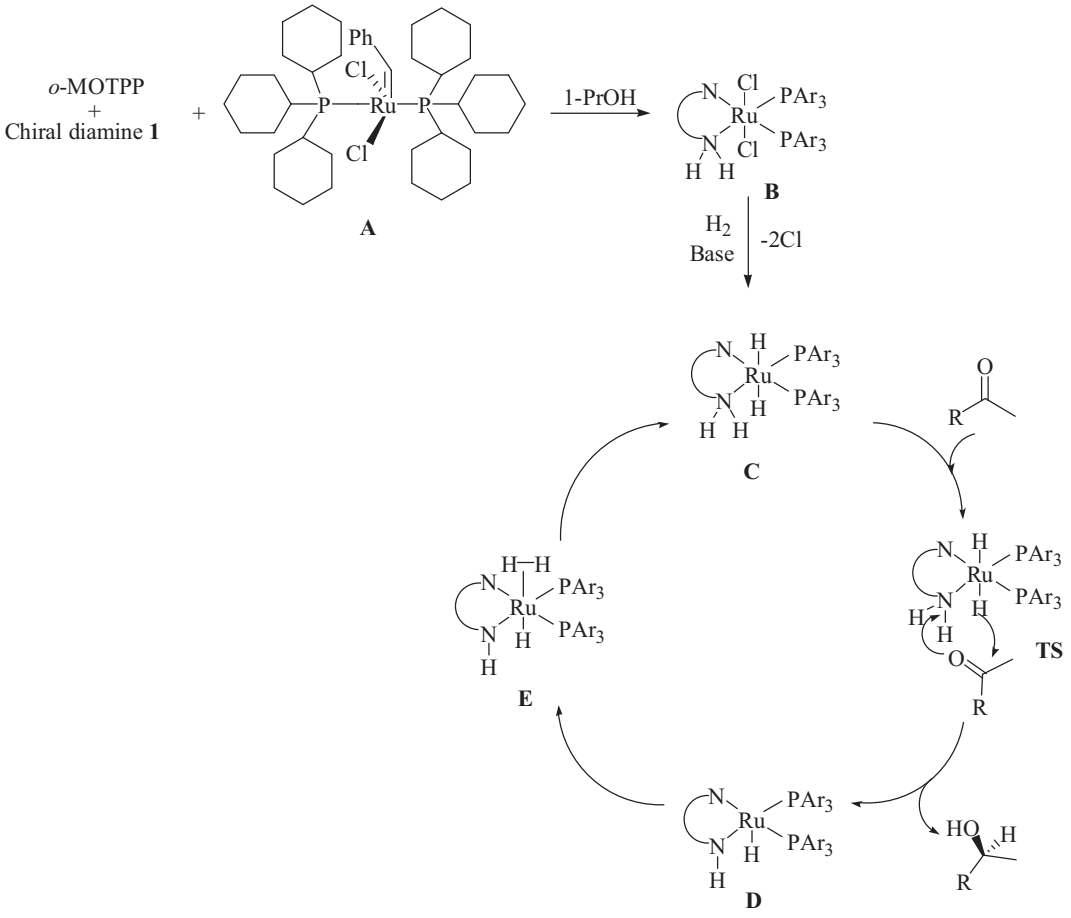


Scheme 1. Scope of the asymmetric hydrogenation of ketones. (substrate/Ru/chiral diamine **1**/*o*-MOTPP = 200/1/2/1, ketones: 0.428 mol/L, LiOH: 0.1 mol/L, 1-PrOH: 2 mL. 30 °C, 6 MPa, 2 h; [b] 40 °C, [c] substrate/Ru = 100/1, [d] substrate/Ru = 50/1)

properties and steric effect. It is worth noting that the steric effect of the group on the phenyl ring had an important influence on the conversion. *Para*-OCH_3 substituted substrate and 1-phenyl-1-butanone also performed well, giving the corresponding hydrogenation product with 92.6% and 88.1% ee, respectively. Encouraged by the excellent enantioselectivities attained in these initial studies, we next extended our researches to involve asymmetric hydrogenation of heteroaromatic ketones. 2-acetylthiophene proceeded efficiently with 88.5% ee. Acetylthiophene derivates bearing substituted groups such as methyl, chloro, bromo at *ortho* or *meta* positions, also reacted to afford the

desired corresponding secondary alcohol in high ee values. In particular, in the case of hydrogenation of 2-acetyl-5- methylthiophene, 97.3% ee were obtained. Due to the steric hindrance, both 2-propionyl thiophene and 2-butyryl thiophene were reduced in lower conversion. Furthermore, other heteroaromatic ketones, such as 2-acetylfuran, 2-butyrylfuran, 2-methyl-5-propionyl-furan and 2-acetyl-5-methylfuran were also reduced with good enantioselectivities under mild conditions, furnishing 81.5–88.7% ee. As is well known, acetyl pyridines were more difficult to hydrogenate due to the strong coordination ability of nitrogen atom in previous studies [32]. To our delight, 3-acetyl pyridines and 4-acetyl pyridines were hydrogenated well under reducing S/C to 100/1, 83.9 and 80.1% ee obtained with moderate to good conversion, respectively. The results disclosed that a wide range of aromatic and heteroaromatic ketones can be hydrogenated to afford various chiral alcohols with good to excellent enantioselectivities. (See Scheme 1).

We proposed a mechanism, similar to the mechanism described by Morris and co-workers for asymmetric hydrogenation with Ru complex, chiral diamine and achiral phosphine ligand, in which the ultimate catalyst that reacted with the ketones may be a ruthenium dihydride (structure **C** in Scheme 2) [33–35]. First, the chiral diamine **1** and *o*-MOTPP reacted with complex **A** to form complex **B**. Under the influence of base and hydrogen, the ruthenium complex **B** lost two chlorine atoms to transform into ruthenium dihydride complex **C**. Then, the ruthenium dihydride **C** transferred a hydridic Ru-H and a protic N-H unit to the carbonyl group of the ketones through the transition state **TS** to generate chiral alcohol. And the ruthenium complex lost one molecule of H_2 produce to the ruthenium complex **D**. Finally, the ruthenium dihydride **C** was regenerated under hydrogen atmosphere. The mechanism was verified by ^1H and ^{31}P NMR spectroscopy. Fig. 1 show ^1H spectra taken without H_2 to the solution of in situ generated complex **B** in 1-PrOH and ^1H spectra of the complex **A** and chiral diamine **1**. The ^1H NMR spectrum exhibits single peak at $\delta = 19.91$ ppm, which belong to Phenyl vinyl group of the complex **A** disappeared in the beginning. At the same time, a new single peak at $\delta = 5.49$ ppm appeared, which maybe the signal of coordination between chiral diamine **1** and ruthenium. These indicated the formation of ruthenium complex **B**. In addition, the ^{31}P NMR spectra of the ruthenium complex A, chiral diamine 1 and *o*-MOTPP taken without H_2 to the solution and ^{31}P NMR spectra of the complex A were collected (Fig. 2). The ^{31}P NMR spectrum of ruthenium complex A exhibits one singlet at $\delta = 35.71$ ppm (s). After the complex A, chiral diamine 1 and *o*-MOTPP mixed without H_2 to the solution, the singlet of ruthenium complex A disappeared and the ^{31}P NMR spectrum exhibits two new singlets at $\delta = 33.27$ ppm (s, major) and 33.45 ppm (s, minor). These may indicate the phosphine ligands coordinate to form the complex B. Fig. 3 and Fig. 4 show ^1H and ^{31}P NMR spectra taken at 2 min to 2 h after introducing H_2 to the solution of in situ generated ruthenium hydride in 1-PrOH. After treatment with H_2 for 2 min at ambient atmosphere, the ^1H NMR spectrum exhibits signal at $\delta = -12.45$ ppm, and the ^{31}P NMR spectrum exhibits two singlets at $\delta = 53.27$ ppm (s, major) and 31.14 ppm (s, minor). These may indicate the formation of ruthenium dihydride complexes **C**. After 30 min, some weak signals appeared at $\delta = -16.50$ ppm in the ^1H NMR spectrum, and at $\delta = 73.17$ ppm in the ^{31}P NMR spectrum, showing the formation of ruthenium monohydride complexes **D**. In addition, signals for the early formed ruthenium dihydride complexes **D** became weak in the ^1H NMR spectrum with the increase of reaction time. Furthermore, the new generated minor signals in both the ^1H NMR spectrum and ^{31}P NMR spectrum show the formation of other ruthenium hydride complexes.



Scheme 2. Proposed mechanism for the asymmetric hydrogenation.

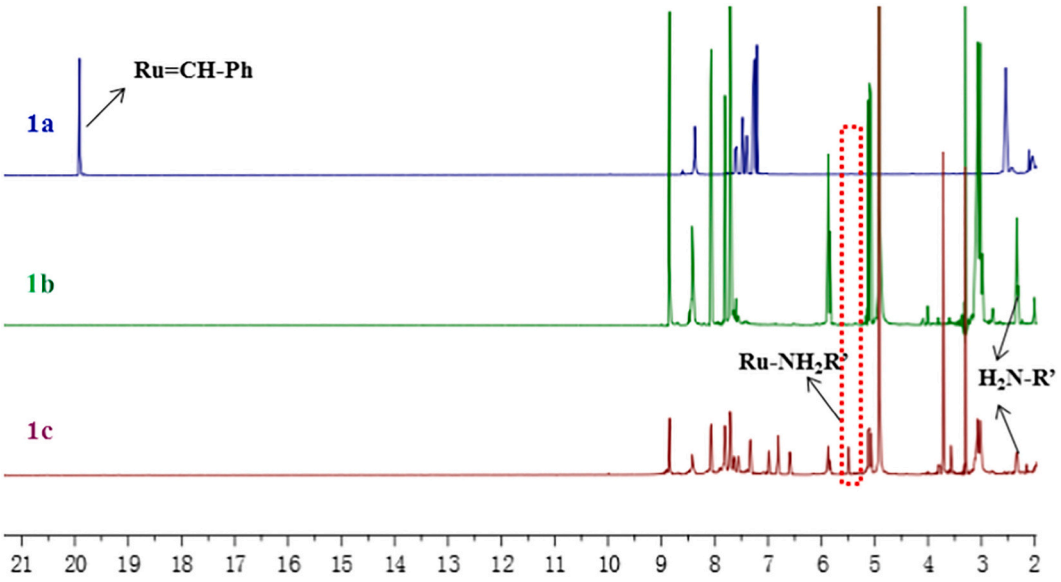


Fig. 1. ^{1}H spectra taken without H_2 to the solution and ^{1}H spectra of the complex **A** and chiral diamine **1**.

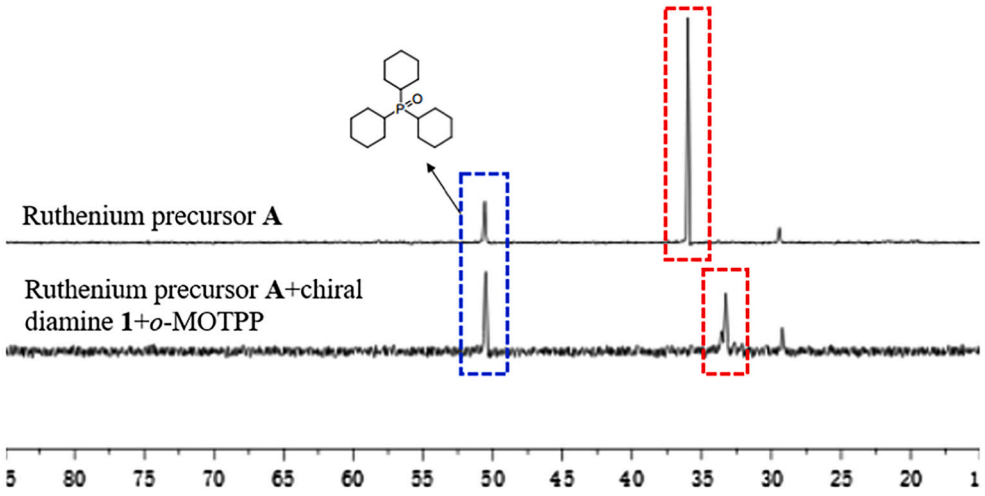


Fig. 2. ^{31}P NMR spectra of the complex **A**, chiral diamine **1** and *o*-MOTPP taken without H_2 to the solution and ^{31}P NMR spectra of the complex **A**.

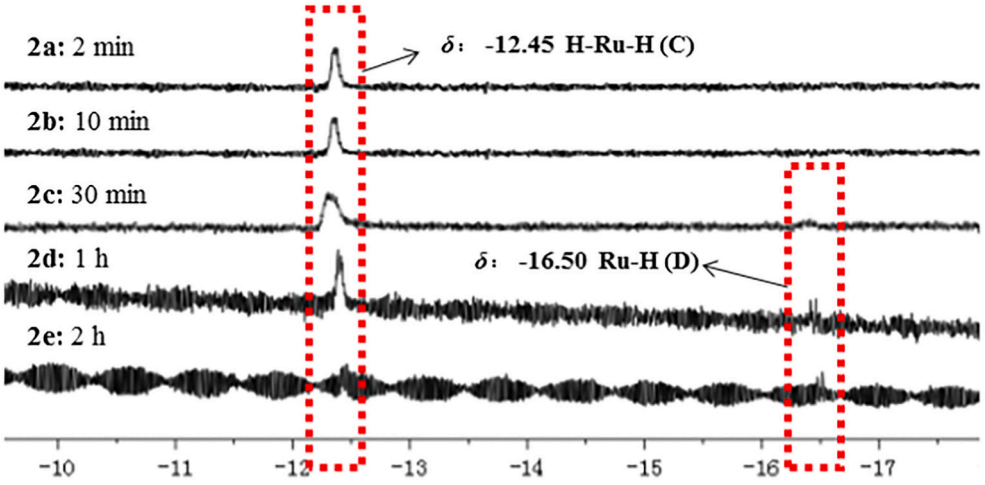


Fig. 3. ^{1}H NMR spectra taken at 2 min to 2 h after introducing H_2 to the solution.

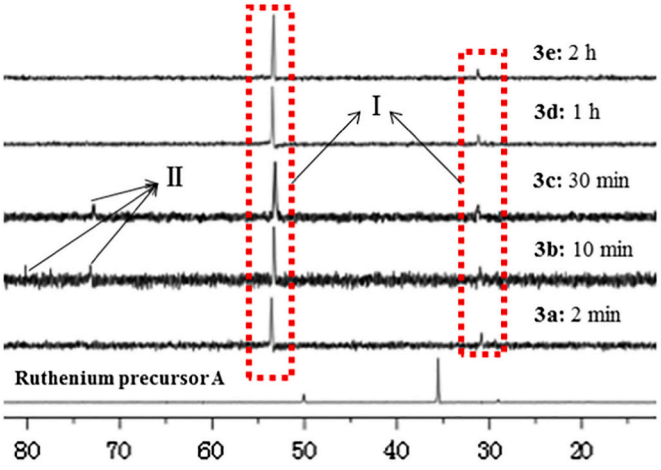


Fig. 4. ^{31}P NMR spectra taken at 2 min to 2 h after introducing H_2 to the solution.

4. Conclusion

In conclusion, we have successfully developed a ruthenium catalyst bearing chiral diamine and inexpensive achiral phosphine that are highly efficient for the asymmetric hydrogenation of various ketones. The reaction provides a readily accessible method for the synthesis of chiral secondary alcohols in excellent enantioselectivities and makes this asymmetric hydrogenation highly practical. In addition, the proposed mechanism for the asymmetric hydrogenation was verified by ^{1}H and ^{31}P NMR spectroscopy.

Credit author statement

Chun Li: Conceptualization; Funding acquisition; Writing - review & editing; Project administration; **Mengna Wang and Ling Zhang:** Investigation; Data curation; Formal analysis; Writing - original draft; **Hao Sun, Qian Chen and Jian Jiang:** Software; Supervision; Validation; **Lin Zhang:** Methodology; **Li Li and Linlin Li:** Visualization; Resources.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.catcom.2021.106303.

References

[1] K. Abdur-Rashid, R. Guo, A.J. Lough, R.H. Morris, D. Song, Adv. Synth. Catal. 347 (2005) 571.
[2] R. Guo, R.H. Morris, D. Song, J. Am. Chem. Soc. 127 (2005) 516.
[3] Y. Xu, N.W. Alcock, G.J. Clarkson, G. Docherty, G. Woodward, M. Wills, Org. Lett. 6 (2004) 4105.
[4] Y. Xu, G.C. Clarkson, G. Docherty, C.L. North, G. Woodward, M. Wills, J. Organomet. Chem. 70 (2005) 8079.
[5] T. Ohkuma, H. Ooka, S. Hashiguchi, T. Ikariya, R. Noyori, J. Am. Chem. Soc. 117 (1995) 2675.
[6] T. Ohkuma, D. Ishii, H. Takeno, R. Noyori, J. Am. Chem. Soc. 122 (2000) 6510.
[7] P. Cao, X. Zhang, J. Organomet. Chem. 64 (1999) 2127.
[8] W. Li, X. Sun, L. Zhou, G. Hou, S. Yu, X. Zhang, J. Organomet. Chem. 74 (2009) 1397.
[9] M.J. Burk, W. Hems, D. Herzberg, C. Malan, A. Zanotti-Gerosa, Org. Lett. 2 (2000) 4173.
[10] C. Chen, R.A. Reamer, J.R. Chilenski, C.J. McWilliams, Org. Lett. 5 (2003) 5039.
[11] J.H. Xie, L.X. Wang, Y. Fu, S.F. Zhu, B.M. Fan, H.F. Duan, Q.L. Zhou, J. Am. Chem. Soc. 125 (2003) 4404.
[12] J.B. Xie, J.H. Xie, X.Y. Liu, W.L. Kong, S. Li, Q.L. Zhou, J. Am. Chem. Soc. 132 (2010) 4538.
[13] Y. Ma, H. Liu, L. Chen, X. Cui, J. Zhu, J. Deng, Org. Lett. 5 (2003) 2103.
[14] K. Junge, K. Mçller, B. Wendt, S. Das, D. Gçrdes, K. Thurow, M. Beller, Chem. Asian J. 7 (2012) 314.
[15] M. Ito, Y. Shibata, A. Watanabe, T. Ikariya, Synlett 10 (2009) 1621.
[16] M.L. Han, X.P. Hu, J.D. Huang, L.G. Chen, Z. Zheng, Tetrahedron Asymmetry 22 (2011) 222.
[17] C.A. Madrigal, A. García-Fernández, J. Gimeno, E. Lastra, J. Organomet. Chem. 693 (2008) 2535.
[18] L. Zeng, F. Wu, Y.Y. Li, Z.R. Dong, J.X. Gao, J. Organomet. Chem. 762 (2014) 34.
[19] O. Altan, M.K. Yılmaz, J. Organomet. Chem. 861 (2018) 252.
[20] Z.R. Dong, Y.Y. Li, J.S. Chen, B.Z. Li, Y. Xing, J.X. Gao, Org. Lett. 7 (2005) 1043.
[21] H. Zhang, C.B. Yang, Y.Y. Li, Z.R. Dong, J.X. Gao, H. Nakamura, K. Murata, T. Ikariya, Chem. Commun. 34 (2003) 142.
[22] W. Wu, S. Liu, M. Duan, X. Tan, C. Chen, Y. Xie, Y. Lan, X.Q. Dong, X. Zhang, Org. Lett. 12 (2016) 2938.
[23] C. Qin, C.J. Hou, H. Liu, Y.J. Liu, D.Z. Huang, X.P. Hu, Tetrahedron Lett. 59 (2018) 719.
[24] W.J. Zhang, S.H. Ruan, W.Y. Shen, Z. Wang, D.L. An, Y.Y. Li, J.X. Gao, Catal. Commun. 119 (2018) 153.
[25] M. Boukachabia, L. Aribi-Zouioueche, O. Riant, J. Organomet. Chem. 868 (2018) 95.
[26] R. H, Crabtree in the Organometallic Chemistry of the Transition Metals, Wileyinterscience, New York, 2001.
[27] C. Li, L. Zhang, Y. Du, X.L. Zheng, H.Y. Fu, H. Chen, R.X. Li, Catal. Commun. 28 (2012) 5.
[28] X. Lu, M. Wang, L. Zhang, J. Jiang, L. Li, X. Gao, L. Zhang, C. Li, Tetrahedron Lett. 61 (2020) 151661.
[29] C. Li, X. Lu, M. Wang, L. Zhang, J. Jiang, S. Yan, Y. Yang, Y. Zhao, L. Zhang, Tetrahedron Lett. 61 (2020) 152356.
[30] H. Zhou, H. Huang, ChemCatChem 5 (2013) 2253.
[31] S. Takebayashi, N. Dabral, M. Miskolzie, S.H. Bergens, J. Am. Chem. Soc. 133 (2011) 9666.
[32] W.Y. Shen, Y.Y. Li, Z.R. Dong, J.X. Gao, Synthesis 14 (2009) 2413.
[33] K. Abdur-Rashid, S.E. Clapham, A. Hadzovic, J.N. Harvey, A.J. Lough, R.H. Morris, J. Am. Chem. Soc. 124 (2002) 15104.
[34] R. Abbel, K. Abdur-Rashid, M. Faatz, A. Hadzovic, A.J. Lough, R.H. Morris, J. Am. Chem. Soc. 127 (2005) 1870.
[35] M. Zimmer-De Iuliis, R.H. Morris, J. Am. Chem. Soc. 131 (2009) 11263.