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Asymmetric hydrogenation of aromatic ketones using new chiral-bridged diphosphine/diamine–Ru(II) complexes

Yu Ming Cui [a,c], Lai Lai Wang [a,*], Fuk Yee Kwong [b,*], Wei Sun [a]

[a] State Key Laboratory for Oxo Synthesis and Selective Oxidation, Lanzhou Institute of Chemical Physics, Chinese Academy of Sciences, Lanzhou 730000, China
[b] Open Laboratory of Chirotechnology of the Institute of Molecular Technology for Drug Discovery and Synthesis and Department of Applied Biology and Chemical technology, The Hong Kong Polytechnic University, Hong Kong, China
[c] Graduate University of Chinese Academy of Sciences, Beijing 100039, China

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Dedicated to Professor Albert S. C. Chan on the occasion of his 60th birthday.

Abstract

A series of chiral secondary alcohols were easily prepared by means of asymmetric hydrogenation of prochiral aromatic ketones using a new ((R_{ax})-BuP)/(*R*,*R*)-DPEN–Ru(II) complex catalyst system. The hydrogenation of 2-methylacetophenone in *n*-butanol (*t*-BuOK/Ru = 45.6/1, S/C = 500, 20 atm. of H_2, 20 °C, 48 h) afforded (*S*)-1-(2′-methylphenyl)ethanol in 92% *ee* and >99% conversion.

Keywords: Asymmetric hydrogenation; Chiral alcohols; Diphosphine ligand; Ruthenium complexes; Diamine

Chiral alcohols may be used in the industrial production of synthetic intermediates for some important antibiotics [1]. Asymmetric hydrogenation of prochiral ketones has been exceedingly successful and proved to be one of the most efficient protocols for accessing a variety of chiral secondary alcohols since Noyori and co-workers developed the BINAP–ruthenium–diamine complexes as a highly effective catalyst for this type of enantioselective transformation [2]. Inspired by the intrinsic advantages, such as operational simplicity and environmental friendliness, of this methodology, a continuous searching of a higher efficiency of chiral ligands for better stereocommunication has been made [3]. Recently, Zhang and our group independently reported a new and highly modular approach for preparing axially chiral diphosphine ligand family [4]. In particular, the chiral-bridged atropisomeric biphenyl diphosphine ligands, demonstrated by our group, have found numerous applications in transition metal-catalyzed asymmetric transformation, including the catalytic enantioselective hydrogenations of *N*-substituted allyphthalimides, α-and β-ketoesters, 2-(6′-methoxy-2′-naphthyl)-propenoic acid, alkyl-substituted β-dehydroamino acids, and *N*-heteroaromatic compounds [4b]. Besides, the C_3*-Tunephos/diamine–Ru(II) complex afforded remarkable reactivity and

* Corresponding authors.
E-mail addresses: wll@licp.cas.cn (L.L. Wang), bcfyk@inet.polyu.edu.hk (F.Y. Kwong).

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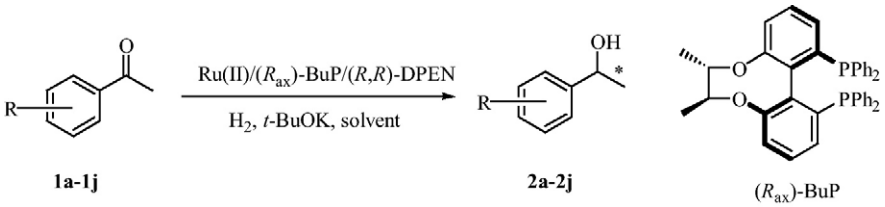
Table 1
Asymmetric hydrogenation of acetophenone (**1a**, R = H).[a]



1a-1j **2a-2j** (R_{ax})-BuP

Entry	S/C[b]	Solvent	Temperature (°C)	Time (h)	Conv (%)[c]	*ee*% (config.)[d]
1	1000	CH_3OH	20	20	46	55 (*S*)
2	1000	2-PrOH	20	23	>99	79 (*S*)
3	1000	2-PrOH	28	18	>99	75 (*S*)
4	1000	*n*-BuOH	20	22	>99	80 (*S*)
5	5000	*n*-BuOH	20	21	38	79 (*S*)
6	3000	*n*-BuOH	20	21	99	80 (*S*)

[a] Reactions were performed with ~1.2 mol/L solutions of **1a** in solvent with *t*-BuOK/Ru = 45.6/1 at 20 atm initial hydrogen pressure.
[b] Substrate-to-catalyst molar ratio.
[c] Determined by capillary GC (HP-5MS).
[d] The *ee* values were determined by chiral GC (Chrompack Chirasil-DEX CB columns). The absolute configuration was determined by comparison of the retention time with literature data.

excellent enantioselectivities in reduction of ketones [5]. Although the effect on enantio-differentiation using 3,5-dimethylphenyl moiety on phosphorus donor has not been explicitly established, empirical evidences showed that the needs of xylyl moieties in a number of chiral diphosphines were beneficial [3e,3g,5]. Based on the fact that subtle changes in geometric, steric, and/or electronic properties of chiral ligands can lead to dramatic variations of reactivity and enantioselectivity, the conformationally rigid yet tunable chiral ligands offer a great advantage and opportunity in optimizing the enantioselectivity of a reaction. Thus, we expect that changing the chain length of chiral bridge on diphosphine ligand will cause major influence on the performance of catalyst system [6]. Herein, we report our preliminary results on the asymmetric hydrogenation of aromatic ketones using C_2*-Tunephos((R_{ax})-BuP)/diamine–Ru(II) complex.

By employing the method reported by Doucet [7], the catalyst was prepared by reacting (R_{ax})-BuP with $[Ru(benzene)Cl_2]_2$ in DMF at 100 °C, followed by the addition of (*R*,*R*)-DPEN (DPEN = 1,2-diphenylethylenediamine). After removing of solvent, the resulting diphosphine–ruthenium–diamine complex was used as the precatalyst directly in the hydrogenation reactions without further purification. Indeed, the ^{31}P NMR showed only a single peak at 47.5 ppm in $CDCl_3$ that represented essentially completed coordination of ligand to Ru center. The hydrogenation of acetophenone **1a** was taken as the model reaction to examine the reaction parameters and the results were listed in Table 1. Notably, an obvious solvent effect was observed and under otherwise identical conditions. Methanol gave poor results with only 46% conversion and 55% *ee* (Table 1, entry 1). In contrast, hydrogenation of acetophenone proceeded completely in isopropanol with 79% *ee* at 20 °C. Moreover, the optical outcome of 75% *ee* was obtained at 28 °C, indicating that the enantioselectivity of the hydrogenation reaction was slightly sensitive to temperature (Table 1, entries 2 and 3). *n*-Butanol provided slight better ee values, when compared to isopropanol which is normally used as a common solvent in asymmetric hydrogenation of ketones (Table 1, entries 2 and 4). Increasing the ratio of substrate to catalyst from 3000 to 5000 led to only 38% conversion of acetophenone to 1-phenylethanol but the enantioselectivity of the product was almost not affected (Table 1, entries 5 and 6), which was comparable to that obtained using C_3*-Tunephos/DPEN–Ru(II) complex system under similar conditions [5].

In order to explore the potential utilities of the catalyst system, a variety of substituted aryl methyl ketones were submitted to hydrogenation. As shown in Table 2, all selected substrates were hydrogenated smoothly with >99% conversion and moderate to good enantioselectivity. It was noted that the position of substituents at the phenyl ring had dramatic effects on reactions. Substrate possessing *ortho*-substituent showed lower reactivity in hydrogenation and they could only be hydrogenated at a relatively higher catalyst loading or prolonged reaction time. Nevertheless, the introduction of either methyl, or methoxy, or bromo group to *para*-position of aromatic ketones had almost no effect

Table 2
Asymmetric hydrogenation of ketones.[a]

Entry	Ketone	R	S/C[b]	Time (h)	Conv (%)[b]	*ee*% (config.)[b]
1	**1b**	*p*-CH_3	3000	45	>99	81 (*S*)
2	**1c**	*p*-Br	3000	41	>99	68 (*S*)
3	**1d**	*p*-OCH_3	3000	40	>99	83 (*S*)
4	**1e**	*m*-CH_3	2000	64	>99	84 (*S*)
5	**1f**	*m*-Br	2000	22	>99	75 (*S*)
6	**1g**	*m*-OCH_3	2000	44	>99	83 (*S*)
7	**1h**	*o*-CH_3	500	48	>99	92 (*S*)
8	**1i**	*o*-Br	500	48	>99	89 (*S*)
9	**1j**	*o*-OCH_3	500	48	>99	58 (*S*)

[a] Reactions were performed with ~1.2 mol/L solutions of ketones in *n*-butanol with *t*-BuOK/Ru = 45.6/1 at 20 °C and 20 atm initial hydrogen pressure.
[b] See Table 1.

on reaction activity. Among the selected substitutents, the electron-withdrawing group activated the substrate and the prochiral ketone was hydrogenated within a shorter reaction time under the same catalyst loading (Table 2, entries 4–6), which is in consistent with previous findings [3e]. On the other hand, these substitutents had different influence on enantioselectivity. Changing the methyl and bromo group position from *para*- to *meta*- to *ortho*- led to consecutively increased enantioselectivity. However, it was found that the *ortho*-methoxy substituted aromatic ketone gave the lowest *ee* value, among the substrate containing methoxy group at different positions.

In conclusion, we presented a new and efficient catalyst system which was applicable in asymmetric hydrogenation of aromatic ketones [8]. The substitutent effects on substrate affecting the reaction reactivity and enantioselectivity were studied in detail. Moderate to good enantioselectivity were obtained for a variety of substrates under complete conversion. Further modification of substitutents on phosphorus donor on the chiral supporting ligands and their application in asymmetric hydrogenation of other prochiral substrates are currently underway.

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References

[1] (a) W.K. Hagmann, J. Med. Chem. 51 (2008) 4359;
(b) M.M. Zhao, J.M. McNamara, G.J. Ho, et al. J. Org. Chem. 67 (2002) 6743.
[2] (a) R. Noyori, Asymmetric Catalysis in Organic Synthesis, Wiley, New York, 1993;
(b) E.N. Jacobsen, A. Pfaltz, H. Yamamoto (Eds.), Comprehensive Asymmetric Catalyses, Springer, Berlin, Germany, 1999;
(c) I. Ojima (Ed.), Catalytic Asymmetric Synthesis, 2nd ed., Wiley, New York, 2000;
(d) S. Bhaduri, D. Mukesh, Homogeneous Catalysis Mechanisms and Industrial Applications, Wiley, New York, 2000;
(e) G.Q. Lin, Y.M. Li, A.S.C. Chan, Principles and Applications of Asymmetric Synthesis, Wiley, New York, 2001.
[3] (a) R. Noyori, T. Ohkuma, Angew. Chem. Int. Ed. 40 (2001) 40;
(b) R. Noyori, Adv. Synth. Catal. 345 (2003) 15;
(c) W.K. Hagmann, J. Med. Chem. 519 (2008) 4359;
(d) M.J. Burk, W. Hems, D. Herzberg, et al. Org. Lett. 2 (2000) 4173;
(e) J. Wu, H. Chen, W.H. Kwok, et al. J. Org. Chem. 67 (2002) 7908;
(f) J. Wu, J.X. Ji, R.W. Guo, et al. Chem. Eur. J. 9 (2003) 2963;
(g) J.H. Xie, L.X. Wang, Y. Fu, et al. J. Am. Chem. Soc. 125 (2003) 4404;
(h) A.G. Hu, H.L. Ngo, W.B. Lin, Org. Lett. 6 (2004) 2937.
[4] (a) X.F. Sun, L. Zhou, W. Li, et al. J. Org. Chem. 73 (2008) 1143;
(b) L. Qiu, F.Y. Kwong, J. Wu, et al. J. Am. Chem. Soc. 128 (2006) 5955.
[5] W. Li, X.F. Sun, L. Zhou, et al. J. Org. Chem. 74 (2009) 1397.
[6] (a) Z.G. Zhang, H. Qian, J. Longmire, et al. J. Org. Chem. 65 (2000) 6223;
(b) S.L. Wu, W.M. Wang, W.J. Tang, et al. Org. Lett. 4 (2002) 4495.
[7] H. Doucet, T. Ohkuma, K. Murata, et al. Angew. Chem. Int. Ed. 37 (1998) 1703.

[8] Typical procedure of asymmetric hydrogenation of **1a**: The precatalyst (0.0025 mmol) and *t*-BuOK (0.114 mmol) was dissolved in degassed *n*-butanol (2 mL) in a 25-mL schlenk flask, substrate (2.5 mmol) were added *via* syringe. The resulting mixture was stirred for 20 min before being transferred into an autoclave, and the autoclave was purged with H_2 (3× 10 atm) and charged with H_2 (20 atm). After stirring at 20 °C for 22 h, the H_2 was carefully released. The reaction solution was purified by a silica gel column to give the corresponding hydrogenation product, which was then directly analyzed by chiral GC to determine the enantiomeric excess. The hydrogenation product was also characterized by ^{1}H NMR (Table 1, entry 4, (*R*)-1-phenylethanol; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.49 (d, 3H, J = 6.4 Hz), 2.02 (br, 1H), 4.88 (q, 1H, J = 6.4 Hz), 7.25–7.29 (m, 1H), 7.29–7.39 (m, 4H)).