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"Achiral" Benzophenone Ligand for Highly Enantioselective Ru Catalysts in Ketone Hydrogenation

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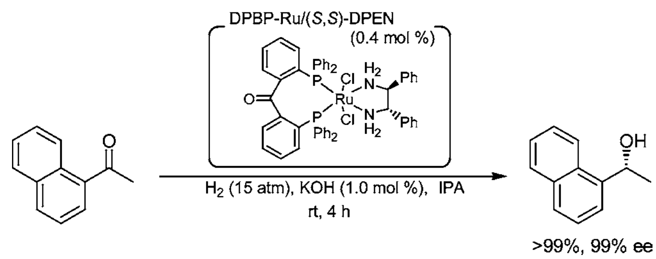
ABSTRACT



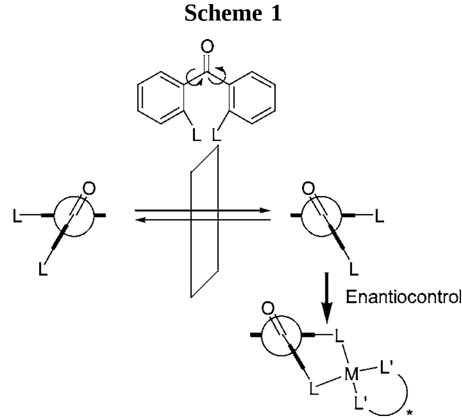
The chirality of an "achiral" benzophenone-based complex can be controlled. The benzophenone-based complex thus controlled affords high enantioselectivity in the catalytic asymmetric ketone hydrogenation (up to 99% ee, >99% yield).

The development of asymmetric catalysts for organic reactions is one of the most challenging subjects in modern science and technology.[1] Generally, asymmetric catalysis employs metal complexes bearing chiral and atropisomeric[2] (originating from *atropos* in Greek[3]) ligands, normally in enantiopure forms.

Inherently, achiral or racemic ligands provide only racemic products. However, asymmetric catalysis might be developed via enantiomeric fluctuation or discrimination of conformational chirality of achiral ligands.[4] Indeed, the racemic BIPHOS ligand was recently reported to spontaneously crystallize and the conglomerate was then used as a chiral ligand.[5] In a fluid phase, however, enantiomeric resolution or control to single conformational chirality is rather difficult due to thermal fluctuations and/or molecular diffusion.[6]

We report here enantiocontrol of achiral benzophenone ligands[7,8] in the solution phase and the use of the metal complexes for highly enantioselective catalysis[9] of ketone hydrogenation[10] (up to 99% ee, 99% yield) (Scheme 1).

Scheme 1



(1) (a) Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H. *Comprehensive Asymmetric Catalysis*; Springer: Berlin, Germany, 1999; Vols. 1−3. (b) *Transition Metals for Organic Synthesis*; Beller, M., Bolm, C., Eds.; VCH: Weinheim, Germany, 1998. (c) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994. (d) Brunner, H.; Zettlmeier, W. *Handbook of Enantioselective Catalysis*; VCH: Weinheim, Germany, 1993. (e) *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, 1993 and 2000; Vols. I and II.

(2) Kuhn, W. *Stereochemie*; Freudenberg, K., Ed.; Franz Deuticke: Leipzig, Germany, 1933; pp 803−824.

(3) The word *atropos* consists of "*a*" meaning "not" and "*tropos*" meaning "turn" in Greek. Therefore, the chirally rigid or flexible nature of a ligand can be called *atropos* or *tropos*, respectively. Mikami, K.; Aikawa, K.; Yusa, Y.; Jodry, J. J.; Yamanaka, M. *Synlett* **2002**, 1561−1578.

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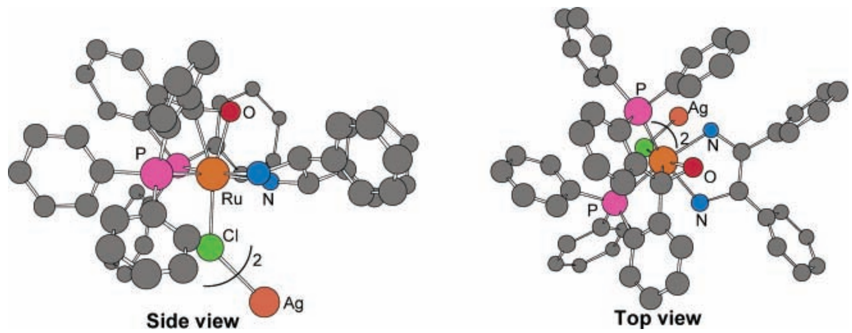


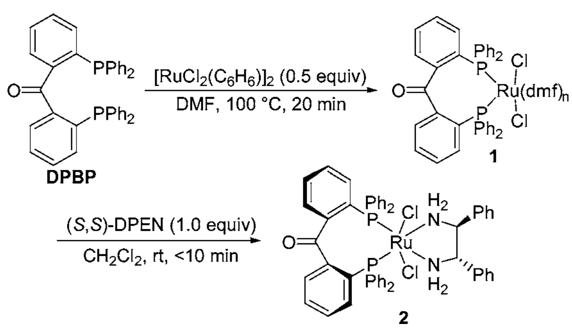
Figure 1. X-ray structure of [RuCl(OTf)(dpbp){(*S*,*S*)-dpen}]$_2$AgOTf (**3**).

The asymmetric catalysts are generally metal complexes bearing chiral and atropisomeric ligands such as BINAP, which usually allow the C_2-symmetric metal complexes for enantiocontrol.[11]

Achiral and *tropos* 2,2′-bis(diphenylphosphino)benzophenone (DPBP) might possess conformational chirality such as BINAP. Upon addition of DPBP to [RuCl$_2$(C$_6$H$_6$)]$_2$, RuCl$_2$(dpbp)(dmf)$_n$ complex **1** was obtained.

The chiral control of RuCl$_2$(dpbp)(dmf)$_n$ complex **1** by (1*S*,2*S*)-(−)-1,2-diphenylethylenediamine ((*S*,*S*)-DPEN) led to the formation of enantiomerically pure RuCl$_2$(dpbp)[(*S*,*S*)-dpen] complex **2** as shown in the solution NMR (Scheme 2). The single crystal of RuCl$_2$(dpbp)[(*S*,*S*)-dpen] (**2**) was

Scheme 2

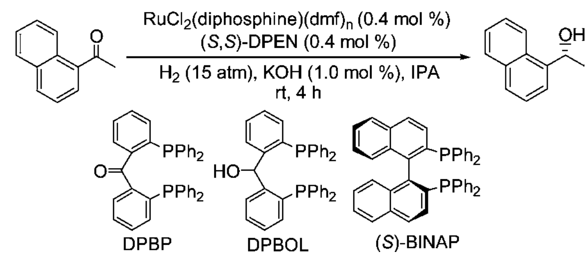


not obtained. Fortunately, however, the single crystal of the monotriflate derivative, [RuCl(OTf)(dpbp){(*S*,*S*)-dpen}]$_2$AgOTf (**3**), was obtained (Figure 1).

The X-ray analysis of [RuCl(OTf)(dpbp){(*S*,*S*)-dpen}]$_2$AgOTf (**3**)[12] showed the enantiopure structure of this benzophenone-derived diphosphine−metal complex **3**. The top view of Figure 1 shows that the benzophenone skeleton of the DPBP ligand adopts a chiral propeller conformation.

The advantage of the "achiral" and *tropos* benzophenone ligand over the enantiopure *atropos* BINAP counterpart for asymmetric catalysis can be seen in hydrogenation of 1′-acetonaphthone (Table 1). A virtually complete (99% ee, >99% yield) enantioselectivity was attained by the benzophenone catalyst **2**. The enantioselectivity thus obtained is higher than 97% ee obtained by our own hand[13] with the enantiopure BINAP counterpart (Table 1, entry 1 vs entry 3). There was a possibility that hydrogenated DPBP, namely

Table 1. Asymmetric Hydrogenation of 1′-Acetonaphthone



entry	diphosphine	alcohol product conv (%)	alcohol product ee (%)
1	DPBP	>99	99
2	DPBOL	67	66
3[a]	(S)-BINAP	>99	97

[a] Also see ref 10a.

(4) (a) Walsh, P. J.; Lurain, A. E.; Balsells, J. *Chem. Rev.* **2003**, *103*, 3297−3344. (b) Faller J. W.; Lavoie, A. R.; Parr, J. *Chem. Rev.* **2003**, *103*, 3345−3368. (c) Mikami, K.; Yamanaka, M. *Chem. Rev.* **2003**, *103*, 3369−3400.

(5) Tissot, O.; Gouygou, M.; Dallemer, F.; Daran, J. C.; Balavoine, G. A. G. *Angew. Chem., Int. Ed.* **2001**, *40*, 1076−1078.

(6) (a) Toda, F.; Tanaka, K.; Kuroda, R. *Chem. Commun.* **1997**, 1227−1228. (b) Takanishi, Y.; Takezoe, H.; Suzuki, Y.; Kobayashi, I.; Yajima, T.; Terada, M.; Mikami, K. *Angew. Chem., Int. Ed.* **1999**, *38*, 2354−2356.

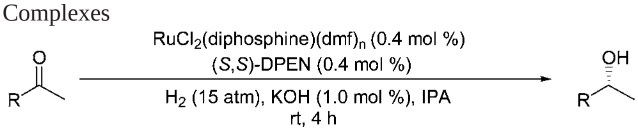
(7) Enantiocontrol of BIPHEP: (a) Mikami, K.; Korenaga, T.; Terada, M.; Ohkuma, T.; Pham, T.; Noyori, R. *Angew. Chem., Int. Ed.* **1999**, *38*, 495−497. (b) Mikami, K.; Aikawa, K.; Yusa, K.; Hatano, M. *Org. Lett.* **2002**, *4*, 91−94. (c) Tudor, M. D.; Becker, J. J.; White, P. S.; Gagné, M. R. *Organometallics* **2000**, *19*, 4376−4384. (d) Becker, J. J.; White, P. S.; Gagné, M. R. *J. Am. Chem. Soc.* **2001**, *123*, 9478−9479. (e) Mikami, K.; Aikawa, K.; Yusa, Y. *Org. Lett.* **2002**, *4*, 95−97. (f) Mikami, K.; Kataoka, S.; Yusa, Y.; Aikawa, K. *Org. Lett.* **2004**, *6*, 3699−3701.

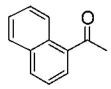
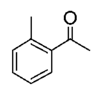
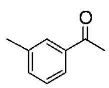
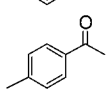
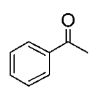
(8) Enantiocontrol of NUPHOS: (a) Doherty, S.; Newman, C. R.; Rath, R. K.; Luo, H.-K.; Nieuwenhuyzen, M.; Knight J. G. *Org. Lett.* **2003**, *5*, 3863−3866. (b) Doherty, S.; Newman, C. R.; Rath, R. K.; van den Berg, J.-A.; Hardacre, C.; Nieuwenhuyzen, M.; Knight J. G. *Organometallics* **2004**, *23*, 1055−1064.

2,2′-bis(diphenylphosphino)benzhydrol (DPBOL), might be involved in the present hydrogenation of 1′-acetonaphthone. However, the hydrogenation with DPBOL was confirmed to be much lower in enantioselectivity than that obtained with DPBP.

The hydrogenation by achiral DPBP is also effective even in the case of ortho-, meta-, or para-substituted acetophenones. DPBP catalyst **2** gave ortho-, meta-, or para-substituted phenethyl alcohols with higher enantioselective (up to 98% ee) than that obtained with BINAP−Ru or tol-BINAP−Ru catalysts (Table 2).

Table 2. Asymmetric Hydrogenation with DPBP−Ru Complexes



Entry	Substrate	Diphosphine	Alcohol product conv (%)	Alcohol product ee (%)
1		**DPBP**	**>99**	**99**
2[a]		(*S*)-BINAP	>99	97
3		**DPBP**	**>99**	**98**
4[b]		(*S*)-BINAP	-	95
5[a]		(*S*)-tol-BINAP	>99	94
6		**DPBP**	**>99**	**92**
7		(*S*)-BINAP	>99	89
8		**DPBP**	**>99**	**91**
9		(*S*)-BINAP	>99	87
10		**DPBP**	**>99**	**90**
11		(*S*)-BINAP	>99	86

[a] Also see: *ref* 10(a).
[b] Also see: *ref* 10(e).

[a] Also see:ref 10a. [b] Also see ref 10e.

In summary, we have uncovered that the chirality of benzophenone complexes can be controlled even in the solution phase. The enantiopure benzophenone complex thus obtained affords even higher enantioselectivity than those attained by the enantiopure BINAP counterpart in the asymmetric catalysis of ketone hydrogenation.

Acknowledgment. We are grateful to Dr. K. Yoza of Nippon Bruker AXS K.K. for X-ray analysis.

Supporting Information Available: Experimental procedures for the preparations of **2** and **3** and for the hydrogenation of ketones, and crystal data for **3** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

OL052936O

(9) (a) Reetz, M. T.; Mehler, G. *Tetrahedron Lett.* **2003**, *44*, 4593−4596. (b) Reetz, M. T.; Li, X. *Angew. Chem., Int. Ed.* **2005**, *44*, 2959−2962. (c) Monti, C.; Gennart, C.; Piarulli, U. *Chem. Commun.* **2005**, 5281−5283.

(10) (a) Ohkuma, T.; Ooka, H.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 2675−2676. (b) Ohkuma, T.; Ooka, H.; Yamakawa, M.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 10417−10418. (c) Ohkuma, T.; Ooka, H.; Yamakawa, M.; Ikariya, T.; Noyori, R. *J. Org. Chem.* **1996**, *61*, 4872−4873. (d) Doucet, H.; Ohkuma, T.; Murata, K.; Yokozawa, T.; Kozawa, M.; Katayama, E.; England, A. F.; Ikariya, T.; Noyori, R. *Angew. Chem., Int. Ed.* **1998**, *37*, 1703−1707. (e) Ohkuma, T.; Koizumi, M.; Doucet, H.; Pham, T.; Kozawa, M.; Murata, K.; Katayama, E.; Yokozawa, T.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1998**, *120*, 13529−13530. (f) Noyori, R.; Ohkuma, T. *Angew. Chem., Int. Ed.* **2001**, *40*, 40−73. (g) Xie, J.-H.; Wang, L.-X.; Fu, Y.; Zhu, S.-F.; Fan, B.-M.; Duan, H.-F.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2003**, *125*, 13529−13530.

(11) (a) BINAP: Noyori, R.; Takaya, H. *Acc. Chem. Res.* **1990**, *23*, 345−350. (b) DET (Diethyl tartrate): Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974−5976. (c) DIOP: Sinou, D.; Kagan, H. B. *J. Organomet. Chem.* **1976**, *114*, 325−337.

(12) Crystal data for [RuCl(OTf)(dpbp){(*S*,*S*)-dpen}]$_2$AgOTf (**3**): formula $C_{107}H_{90.50}AgCl_{9.50}F_{7.50}N_4O_{9.50}P_4Ru_2S_{2.50}$, orthorhombic, space group *P*2(1)2(1)2, $a = 20.9715(16)$ Å, $b = 39.437(3)$ Å, $c = 13.8177(10)$ Å, $\alpha = \beta = \gamma = 90°$, $V = 11428.0(15)$ Å^3, $Z = 4$, and $D = 1.498$ Mg/m^3. The final cycle of full-matrix least-squares on F^2 was based on 26 825 observed reflections and 1448 variable parameters and converged to $R = 0.0754$ and $Rw = 0.2099$. Goodness of fit = 1.145, shift/error = 0.04(3). Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-257768. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (Fax (+44)1223-336-033; E-mail deposit@ccdc.cam.ac.uk).

(13) The enantioselectivity thus obtained is exactly the same as reported: see ref 10a.