ORGANIC LETTERS

2000
Vol. 2, No. 5
659−662

Selective Hydrogenation of Benzophenones to Benzhydrols. Asymmetric Synthesis of Unsymmetrical Diarylmethanols

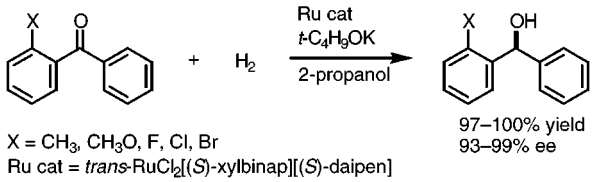
Takeshi Ohkuma,[†,‡] Masatoshi Koizumi,[†] Hideyuki Ikehira,[‡] Tohru Yokozawa,[‡] and Ryoji Noyori*[,†,‡]

Department of Chemistry and Research Center for Materials Science, Nagoya University, Chikusa, Nagoya 464-8602, Japan, and ERATO Molecular Catalysis Project, Japan Science and Technology Corporation, 1247 Yachigusa, Yakusa-cho, Toyota 470-0392, Japan

noyori@chem3.chem.nagoya-u.ac.jp

Received December 30, 1999

ABSTRACT



***trans*-RuCl$_2$[P(C$_6$H$_4$-4-CH$_3$)$_3$]$_2$(NH$_2$CH$_2$CH$_2$NH$_2$) acts as a highly effective precatalyst for the hydrogenation of a variety of benzophenone derivatives to benzhydrols that proceeds smoothly at 8 atm and 23–35 °C in 2-propanol containing *t*-C$_4$H$_9$OK with a substrate/catalyst ratio of 2000–20000. Use of a BINAP/chiral diamine Ru complex effects asymmetric hydrogenation of various ortho-substituted benzophenones and benzoylferrocene to chiral diarylmethanols with consistently high ee.**

Benzhydrols are widely used as intermediates for the commercial synthesis of pharmaceuticals.[1] Although the catalytic hydrogenation of benzophenone derivatives is the simplest way of synthesizing this important class of compounds, the general method remains elusive. Hydrogenation of benzophenone over Pd/C in hexane or a 1:1 mixture of ethanol and acetic acid largely gives diphenylmethane, an over-reduction product,[2] although the catalyst modified with ethylenediamine gives benzhydrols selectively.[3] The Lindlar or some other heterogeneous catalysts,[4] phosphine−Ru complexes,[5] and *t*-C$_4$H$_9$OK as catalyst[6] are known to show high selectivity for carbinol formation, but their scope and limitations are not clear.[7] Therefore, the current industrial processes of producing benzhydrols rely on stoichiomeric

† Nagoya University.
‡ ERATO Molecular Catalysis Project.

(1) Examples include: antihistaminic and -serotonic homochlorcyclizine (Pendse, V. K.; Madan, B. R. *Indian J. Physiol. Pharmacol*. **1969**, *13*, 29−36), antihistaminic oxatomide (Awouters, F.; Niemegeers, C. J. E.; Van den Berk, J.; Van Nueten, J. M.; Lenaerts, F. M.; Borgers, M.; Schellekens, K. H. L.; Broeckaert, A.; De Cree, J.; Janssen, P. A. J. *Experientia* **1977**, *33*, 1657−1659), antihypertensive manidipine (Meguro, K.; Aizawa, M.; Sohda, T.; Kawamatsu, Y.; Nagaoka, A. *Chem. Pharm. Bull*. **1985**, *33*, 3787−3797), antimycotic bifonazole (Regel, E.; Draber, W.; Büchel, K. H.; Plempel, M. Ger. Patent 2 461 406, 1976), and flunarizine, a calcium antagonist (Janssen, P. A. J. Fr. Patent 2 014 487, 1970).

(2) Hydrogenation of benzophenone (182 mg) on 10% Pd/C (20 mg) in hexane (6 mL) at 8 atm H_2 and 28 °C for 18 h gave a 35:65 mixture of benzhydrol and diphenylmethane (total 100% yield), whereas reaction in a 2:1 mixture of C_2H_5OH and CH_3COOH afforded diphenylmethane exclusively.

(3) Sajiki, H.; Hattori, K.; Hirota, K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 4043−4044.

(4) (a) Werbel, L. M.; Elslager, E. F.; Pearlman, W. M. *J. Org. Chem*. **1964**, *29*, 967−968. (b) Gosser, L. W. U.S. Patent 4 302 435, 1981. (c) Kumbhar, P. S.; Rajadhyaksha, R. A. *Stud. Surf. Sci. Catal*. **1993**, *78*, 251−258.

(5) (a) Blum, Y.; Czarkie, D.; Rahamim, Y.; Shvo, Y. *Organometallics* **1985**, *4*, 1459−1461. (b) Linn, D. E., Jr.; Halpern, J. *J. Organomet. Chem*. **1987**, 330, 155−159. (c) Lau, C.-P.; Cheng, L. *J. Mol. Catal*. **1993**, *84*, 39−50.

(6) Walling, C.; Bollyky, L. *J. Am. Chem. Soc*. **1964**, *86*, 3750−3752.

10.1021/ol9904139 CCC: $19.00
Published on Web 02/03/2000

reduction using $NaBH_4$.[8] We here disclose a practical procedure for the hydrogenation of benzophenones using the recently discovered $RuCl_2$(phosphine)$_2$(1,2-diamine) complexes as precatalysts.[9,10] Furthermore, the reaction using a chiral Ru complex effects the enantioselective conversion of appropriately substituted diaryl ketones to chiral diarylmethanols.

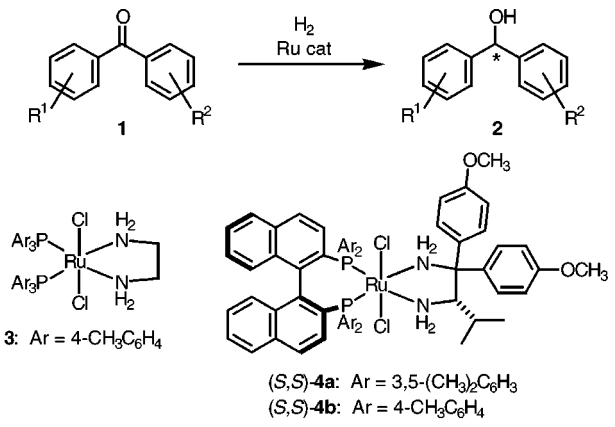
Benzophenone can be hydrogenated to benzhydrol in a nearly quantative yield under 8 atm of hydrogen in 2-propanol containing *trans*-$RuCl_2[P(C_6H_4\text{-}4\text{-}CH_3)_3]_2$ ($NH_2CH_2CH_2NH_2$) (**3**) and *t*-C_4H_9OK ([ketone] = 1 M, ketone/Ru/base = 3000:1:12, 35 °C, 18 h). No diphenylmethane was detected in the product. Table 1 exemplifies the hydrogenation of a range of substituted benzophenones **1** (Scheme 1). Benzhydrol itself and the *p*-CH_3, -phenyl, and -chloro and *p*,*p*′-difluoro derivatives are useful intermediates for syntheses of commercial drugs.[1] The yield of ortho-, meta-, and para-substituted benzhydrol products **2** was consistently high regardless of the substituents, while halogen atoms, CF_3, and methoxy groups in the aromatic ring were left intact.[9] This hydrogenation can be conducted with a substrate/catalyst molar ratio (S/C) as high as 20000. The reaction does not require a homogeneous 2-propanol solution of a ketonic substrate, and sparingly soluble solid benzophenones can be subjected to hydrogenation as a slurry (for example, 200 g of benzophenone in 200 mL of 2-propanol with mechanical strirring at 700 rpm), thereby maintaining a high rate and also minimizing the quantity of solvent.

Table 1. Ruthenium(II)-Catalyzed Hydrogenation of Benzophenones[a]

ketone **1**		conditions		alcohol **2**
R^1	R^2	S/C[b]	concn[c] (M)	yield[d] (%)
H[e]	H	20000	2.7	99
o-CH_3	H	3000	1.5	99
o-Cl	H	2000	0.8	97
m-Cl	H	2000	0.4	98
p-C_6H_5	H	2000	0.4	99[f]
p-CH_3O	H	3000	1.5	99
p-F	H	2000	0.4	99
p-F	*p*-F	3000	1.4	99
p-Cl	H	3000	1.3	100
p-CF_3	H	2000	0.4	99[g]

[a] Unless otherwise stated, reactions were conducted at 8 atm of H_2 for 6−18 h at 28−35 °C using a 2.5−12.5 mmol of the substrate **1** (S) in 2-propanol containing the precatalyst **3** (C) and *t*-C_4H_9OK. [b] Substrate/catalyst molar ratio. Base/**3** = 8. [c] Concentration of the substrate. [d] Determined by GC analysis. [e] Reaction using 200 g (1.1 mol) of benzophenone for 48 h. Base/**3** = 40. [f] Isolated yield. [g] Yield after 1 h.

Scheme 1



(7) Transfer hydrogenation: (a) Kleinfelter, D. C. *J. Org. Chem.* **1967**, *32*, 840−842. (b) Mestroni, G.; Zassinovich, G.; Camus, A.; Martinelli, F. *J. Organomet. Chem.* **1980**, *198*, 87−96. (c) Ram, S.; Spicer, L. D. *Synth. Commun.* **1992**, *22*, 2673−2681. (d) Fujii, A.; Hashiguchi, S.; Uematsu, N.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 2521−2522. (e) Mizushima, E.; Yamaguchi, M.; Yamagishi, T. *Chem. Lett.* **1997**, 237−238.

(8) Another standard method benzhydrol preparetion is via the addition of arylmetals to benzaldehydes.

(9) (a) 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. (b) 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.

(10) See also: (a) Ohkuma, T.; Ooka, H.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 2675−2676. (b) Ohkuma, T.; Ooka, H.; 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) Ohkuma, T.; Ikehira, H.; Ikariya, T.; Noyori, R. *Synlett* **1997**, 467−468. (e) Ohkuma, T.; Doucet, H.; Pham, T.; Mikami, K.; Korenaga, T.; Terada, M.; Noyori, R. *J. Am. Chem. Soc.* **1998**, *120*, 1086−1087. (f) Mikami, K.; Korenaga, T.; Terada, M.; Ohkuma, T.; Pham, T.; Noyori, R. *Angew. Chem., Int. Ed.* **1999**, *38*, 495−497.

(11) Hammett, L. P. *Physical Organic Chemistry*, 2nd ed.; McGraw-Hill: New York, 1970; Chapter 11.

(12) For kinetics of $NaBH_4$ reduction of ketones, see: Brown, H. C.; Wheeler, O. H.; Ichikawa, K. *Tetrahedron* **1957**, *1*, 214−220.

(13) (a) Bowden, K.; Hardy, M. *Tetrahedron* **1966**, *22*, 1169−1174. (b) Bruce, G. T.; Cooksey, A. R.; Morgan, K. J. *J. Chem. Soc., Perkin Trans. 2* **1975**, 551−553.

(14) XylBINAP = 2,2′-bis(di-3,5-xylylphosphino)-1,1′-binaphthyl. Tol-BINAP = 2,2′-bis(di-4-tolylyphosphino)-1,1′-binaphthyl. DAIPEN = 1,1-di(4-anisyl)-2-isopropyl-1,2-ethylenediamine.

(15) For asymmetric reduction of diaryl ketones using silicon- and boron-based hydrides, see: (a) Peyronel, J.-F.; Fiaud, J.-C.; Kagan, H. B. *J. Chem. Res. Miniprint* **1980**, 4057−4080. (b) Brunner, H.; Kürzinger, A. *J. Organomet. Chem.* **1988**, *346*, 413−424. (c) Brown, E.; Penfornis, A.; Bayma, J.; Touet J. *Tetrahedron*: *Asymmetry* **1991**, *2*, 339−342. (d) Brown E, Lézé A, Touet J. *Tetrahedron*: *Asymmetry* **1992**, *3*, 841−844. (e) Shieh, W.-C.; Cantrell, W. R., Jr.; Carlson, J. A. *Tetrahedron Lett.* **1995**, *36*, 3797−3800. (f) Ramachandran, P. V.; Chen, G.-M.; Brown, H. C. *Tetrahedron Lett.* **1996**, *37*, 2205−2208. (g) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998,** *37*, 1986−2012, and references therein.

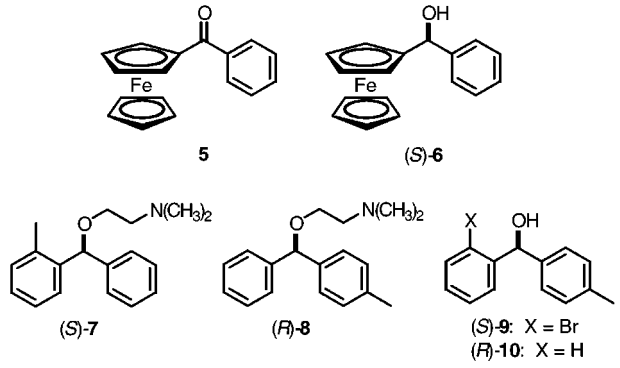
Use of chiral diphosphine/diamine Ru complexes such as *trans*-$RuCl_2$[(*S*)-xylbinap][(*S*)-daipen] [(*S*,*S*)-**4a**][9b,14] allows for asymmetric hydrogenation of unsymmetrical diaryl ketones with an S/C ratio of up to 20000.[15,16] Table 2 lists some examples. A range of ortho-substituted substrates was converted to the corresponding benzhydrols with high ee. For example, the hydrogenation of *o*-methylbenzophenone (**1a**) in the presence of (*S*,*S*)-**4a** (ketone/Ru/*t*-C_4H_9OK = 2000:1:8, 8 atm, 28 °C, 14 h) afforded (*S*)-*o*-methylbenzhydrol [(*S*)-**2a**] in 93% ee in 99% yield.[17,18] In a like manner, the benzophenone **1d** with a chloro substituent, sterically similar but electonically different from methyl, gave the *S* alcohol in 97% ee. Orphenadrine (**7**) is known as an anticholinergic and antihistaminic agent.[19] The dextrorotatory isomer expresses higher activity than its enantiomer;[19b] however, to our knowledge, its absolute configuration has not been determined. The stereochemistry was determined by transforming (*S*)-(+)-**2a** (93% ee) to (*S*)-(+)-**7** hydrochloride, $[\alpha]^{25}_D$ +12.5° (*c* 0.542, CH_3OH), according to the literature.[19a] The hydrogenation of other *o*-methoxy and -halo ketones **1b**, **1c**, and **1e** also displayed a high degree of enantioselection. The sense of asymmetric induction in the reactions of these heteroatom-substituted ketones is identical to that observed with the methyl derivative **1a**, indicating that the possible interaction of the heteroatom to the Ru catalyst is not the origin of enantioselection.[7d,15g] Asymmetric hydrogenation of benzoylferrocene (**5**) with (*S*,*S*)-**4b** gave (*S*)-**6** in 95% ee in 100% yield, which is a useful intermediate for chiral ferrocenyl ligands.[20] The XylBINAP complex (*S*,*S*)-**4a** gave (*S*)-**6** in only 45% ee.

Table 2. Asymmetric Hydrogenation of Diaryl Ketones[a]

ketone				alcohol	
no.	R^1	R^2	catalyst	yield[b] (%)	ee[c] (%)
1a	*o*-CH_3	H	(*S*,*S*)-**4a**	99	93 (*S*)
1b	*o*-CH_3O	H	(*S*,*S*)-**4a**	100	99 (*S*)
1c	*o*-F	H	(*S*,*S*)-**4a**	99	97 (*S*)
1d[d]	*o*-Cl	H	(*S*,*S*)-**4a**	99	97 (*S*)
1d[e]	*o*-Cl	H	(*S*,*S*)-**4a**	99	97 (*S*)
1e	*o*-Br	H	(*S*,*S*)-**4a**	99	96 (*S*)
1f	*o*-Br	*p*-CH_3	(*S*,*S*)-**4a**	99	98 (*S*)
1g	*m*-CH_3	H	(*S*,*S*)-**4a**	98	33 (−)
1h	*p*-CH_3	H	(*S*,*S*)-**4a**	98	8 (*R*)
1i	*p*-CH_3O	H	(*S*,*S*)-**4a**	95	35 (*R*)
1j	*p*-Cl	H	(*S*,*S*)-**4a**	97	9 (*S*)
1k	*p*-CF_3	H	(*S*,*S*)-**4a**	99	47 (*S*)
5[f]	benzoylferrocene		(*S*,*S*)-**4b**	100	95 (*S*)

[a] Reactions were conducted at 8 atm of H_2 using a 2.5 mmol of **1** (0.4−0.8 M) in 2-propanol containing **4** and *t*-C_4H_9OK for 11−15 h at 28 °C. Substrate/catalyst/base = 2000:1:8. [b] Determined by GC or NMR analysis. [c] Determined by chiral HPLC analysis. Absolute configuration is stated in parentheses. [d] Reaction using 10.8 g of **1d** for 47 h at 35 °C. Substrate/catalyst/base = 20000:1:80. [e] Reaction using 101.8 g of **1d** for 55 h at 30 °C. Substrate/catalyst/base = 20000:1:200. [f] Reaction in a 1:4 toluene/2-propanol mixture.

Antihistaminic (*R*)-neobenodine [(*R*)-**8**][19,22] was synthesized by utilizing asymmetric hydrogenation of *o*-bromo-*p*′-methylbenzophenone (**1f**) as a key step where in the bromine atom acts as an enantiodirective functional substituent (Table 2). Thus, the hydrogenation of a 0.8 M solution of **1f** in 2-propanol containing the Ru complex (*S*,*S*)-**4a** and *t*-C_4H_9-OK (ketone/Ru/base = 2000:1:8, 8 atm, 28 °C, 16 h) afforded (*S*)-**9** in 98% ee in 99% yield. Lithiation of the bromo alcohol with 3 equiv of *n*-C_4H_9Li in THF at −78 °C for 3 h followed by hydrolysis and recrystallization from a 20:1 mixture of hexane and ethyl acetate gave (*R*)-**10** in 99.7% ee, $[\alpha]^{25}_D$ +8.65° (*c* 0.780, $CHCl_3$), in 96% yield.[17] This chiral alcohol can readily be converted to (*R*)-**8**.[19]



(16) For catalytic asymmetric addition of $Ti(C_6H_5)(OCH(CH_3)_2)_3$ or $Zn(C_6H_5)_2$ to benzaldehydes, see: (a) Weber, B.; Seebach, D. *Tetrahedron* **1994**, *50*, 7473−7484. (b) Dosa, P. I.; Ruble, J. C.; Fu, G. C. *J. Org. Chem.* **1997**, *62*, 444−445. (c) Bolm, C.; Muñiz, K. *Chem. Commun*. **1999**, 1295−1296. (d) Huang, W.-S.; Pu, L. *J. Org. Chem*. **1999**, *64*, 4222−4223.

(17) (a) Watanabe, M.; Kuwahara, S.; Harada, N.; Koizumi, M.; Ohkuma, T. *Tetrahedron*: *Asymmetry* **1999**, *10*, 2075−2078. (b) Kuwahara, S.; Watanabe, M.; Harada, N.; Koizumi, M.; Ohkuma, T. *Enantiomer*, in press. See also: Harada, N.; Fujita, K.; Watanabe, M. *Enantiomer* **1997**, *2*, 359−366. Harada, N.; Fujita, K.; Watanabe, M. *Enantiomer* **1998**, *3*, 64−70.

(18) A typical procedure of the 100-g scale reaction of *o*-chlorobenzophenone (**1d**) with an S/C ratio of 20000 follows (see also the Supporting Information): The ketone **1d** (101.8 g, 0.47 mol), 2-propanol (150 mL), 1.0 M *t*-C_4H_9OK in *tert*-butyl alcohol (4.7 mL, 4.7 mmol), and solid (*S*,*S*)-**4a** (28.7 mg, 0.0235 mmol) were placed in a 1.5-L stainless steel autoclave. The mixture was degassed, and hydrogen was introduced to a pressure of 8 atm. This mixture was then stirred vigorously at 30 °C for 55 h. The yield and ee of (*S*)-**2d** determined by GC and chiral HPLC analysis were 99 and 97%, respectively. After the solvent was removed under reduced pressure, the residue was distilled to give pure (*S*)-**2d** (97.5 g, 95% yield): bp 138−139 °C/0.3 mmHg; $[\alpha]^{20}_D$ −21.51° (*c* 1.13, $CHCl_3$).[17]

(19) (a) van der Stelt, C.; Heus, W. J.; Nauta, W. T. *Arzneim.-Forsch*. **1969**, *19*, 2010−2012. (b) Rekker, R. F.; Timmerman, H.; Harms, A. F.; Nauta, W. T. *Arzneim.-Forsch*. **1971**, *21*, 688−691.

(20) Ireland, T.; Perea, J. J. A.; Knochel, P. *Angew. Chem., Int. Ed*. **1999**, *38*, 1457−1460.

(21) Zuccarello, F.; Millefiori, S.; Trovato, S. *Can. J. Chem*. **1976**, *54*, 226−230.

(22) Casy, A. F.; Drake, A. F.; Ganellin, C. R.; Mercer, A. D.; Upton, C. *Chirality* **1992**, *4*, 356−366.

Overall, this hydrogenation method allows for a clean, technically simple, and economical synthesis of achiral and chiral benzhydrols from benzophenones.

Acknowledgment. We thank Dr. Chizuko Kabuto, Tohoku University, for the X-ray determination of the structures of the (*R*)-*N*-[1′-(1-naphthyl)ethyl]carbamate of (*S*)-**2c** and the (2*R*,3*R*)-3-phenyl-2,3-epoxypropyl ether of (*S*)-**6**. This work was financially supported in part by grants-in-aid from the Ministry of Education, Science, Sports, and Culture of Japan (Nos. 07CE2004 and 11440188).

Supporting Information Available: Procedures for the hydrogenation of diaryl ketones, GC and HPLC behavior of products, and $[\alpha]_D$ values and an absolute-configuration determination procedure for chiral alcohols. This material is available free of charge via the Internet at http://pubs.acs.org.

OL9904139