

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

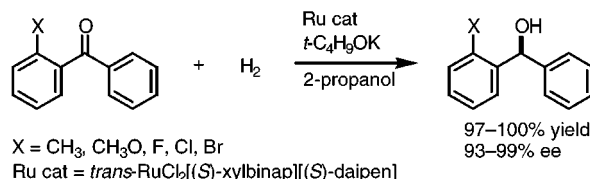
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ABSTRACT



trans-RuCl₂[P(C₆H₄-4-CH₃)₃]₂(NH₂CH₂CH₂NH₂) 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*-C₄H₉OK 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*-C₄H₉OK as catalyst⁶ 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 stoichiometric

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(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 H₂ 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 C₂H₅OH and CH₃COOH afforded diphenylmethane exclusively.

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(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.

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

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

Benzophenone can be hydrogenated to benzhydrol in a nearly quantitative yield under 8 atm of hydrogen in 2-propanol containing *trans*- $\text{RuCl}_2[\text{P}(\text{C}_6\text{H}_4\text{-}4\text{-CH}_3)_3]_2$ ($\text{NH}_2\text{CH}_2\text{-CH}_2\text{NH}_2$) (**3**) and *t*- $\text{C}_4\text{H}_9\text{OK}$ ([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.

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
<i>o</i> -CH ₃	H	3000	1.5	99
<i>o</i> -Cl	H	2000	0.8	97
<i>m</i> -Cl	H	2000	0.4	98
<i>p</i> -C ₆ H ₅	H	2000	0.4	99 ^f
<i>p</i> -CH ₃ O	H	3000	1.5	99
<i>p</i> -F	H	2000	0.4	99
<i>p</i> -F	<i>p</i> -F	3000	1.4	99
<i>p</i> -Cl	H	3000	1.3	100
<i>p</i> -CF ₃	H	2000	0.4	99 ^g

^a Unless otherwise stated, reactions were conducted at 8 atm of H₂ 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*- $\text{C}_4\text{H}_9\text{OK}$. ^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.

tion of a range of substituted benzophenones **1** (Scheme 1). Benzhydrol itself and the *p*-CH₃, -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, CF₃, 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 stirring at 700 rpm), thereby maintaining a high rate and also minimizing the quantity of solvent.

Separate experiments showed that *p*-trifluoromethylbenzophenone was hydrogenated 11 times faster than the *p*-methoxy derivative (5 atm, 28 °C). Thus, in this hydrogenation, electron-withdrawing substituents are favored over donor groups, but the difference is unimportant from a synthetic point of view. The electronic effect of ring substituents on the rate was also examined by competition experiments using an equimolar mixture of benzophenone and a series of para-substituted benzophenones and **3** as catalyst. When the relative rates were plotted against the σ_p constant,¹¹ a linear relationship with a ρ value of +1.78 was obtained (see the Supporting Information). The sensitivity to the electronic influence in the hydrogenation of para-substituted benzophenones is higher than in the reaction of acetophenone derivatives with **3**, which showed $\rho = +0.99$. This value is less than +3.1 observed in the NaBH_4 reduction of acetophenones.^{12,13}

(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 preparation is via the addition of arylmetals to benzaldehydes.

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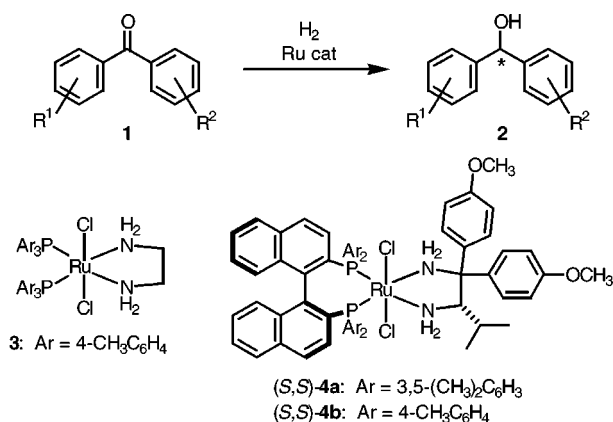
(12) For kinetics of NaBH_4 reduction of ketones, see: Brown, H. C.; Wheeler, O. H.; Ichikawa, K. *Tetrahedron* **1957**, 1, 214–220.

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(14) XylBINAP = 2,2'-bis(di-3,5-xylylphosphino)-1,1'-binaphthyl. Tol-BINAP = 2,2'-bis(di-4-tolylphosphino)-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.

Scheme 1



Use of chiral diphosphine/diamine Ru complexes such as *trans*-RuCl₂[(*S,S*)-xylbinap][(*S,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

Table 2. Asymmetric Hydrogenation of Diaryl Ketones^a

no.	ketone		catalyst	alcohol	
	R ¹	R ²		yield ^b (%)	ee ^c (%)
1a	<i>o</i> -CH ₃	H	(<i>S,S</i>)- 4a	99	93 (<i>S</i>)
1b	<i>o</i> -CH ₃ O	H	(<i>S,S</i>)- 4a	100	99 (<i>S</i>)
1c	<i>o</i> -F	H	(<i>S,S</i>)- 4a	99	97 (<i>S</i>)
1d^d	<i>o</i> -Cl	H	(<i>S,S</i>)- 4a	99	97 (<i>S</i>)
1d^e	<i>o</i> -Cl	H	(<i>S,S</i>)- 4a	99	97 (<i>S</i>)
1e	<i>o</i> -Br	H	(<i>S,S</i>)- 4a	99	96 (<i>S</i>)
1f	<i>o</i> -Br	<i>p</i> -CH ₃	(<i>S,S</i>)- 4a	99	98 (<i>S</i>)
1g	<i>m</i> -CH ₃	H	(<i>S,S</i>)- 4a	98	33 (–)
1h	<i>p</i> -CH ₃	H	(<i>S,S</i>)- 4a	98	8 (<i>R</i>)
1i	<i>p</i> -CH ₃ O	H	(<i>S,S</i>)- 4a	95	35 (<i>R</i>)
1j	<i>p</i> -Cl	H	(<i>S,S</i>)- 4a	97	9 (<i>S</i>)
1k	<i>p</i> -CF ₃	H	(<i>S,S</i>)- 4a	99	47 (<i>S</i>)
5^f	benzoylferrocene		(<i>S,S</i>)- 4b	100	95 (<i>S</i>)

^a Reactions were conducted at 8 atm of H₂ using a 2.5 mmol of **1** (0.4–0.8 M) in 2-propanol containing **4** and *t*-C₄H₉OK 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.

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*-C₄H₉OK = 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 electronically 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, [α]_D²⁵ +12.5° (*c* 0.542, CH₃OH), 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.

As expected, simple meta- and para-substituted benzophenones were hydrogenated with a moderate enantioselectivity. In the presence of (*S,S*)-**4a**, *p*-trifluoromethylbenzophenone (**1k**) gave the *S* alcohol in 47% ee, whereas the *p*-methoxy derivative (**1i**) afforded the *R*-enriched product with 35% ee. Thus, electronic influences of the para substituents and steric effects of the ortho substituents appear to affect the extent of the coplanarity of the benzene rings with C=O function²¹ in the transition state, thereby generating an asymmetric bias.

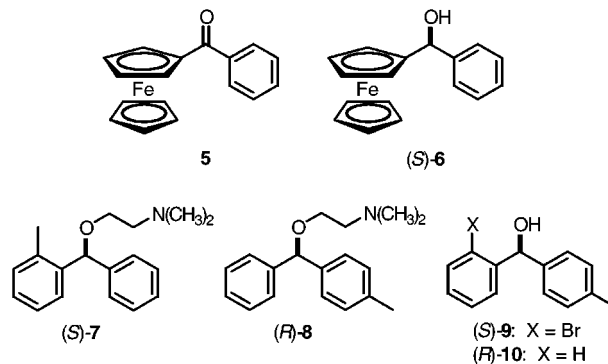
Antihistaminic (*R*)-neobenodine [(*R*)-**8**]^{19,22} was synthesized by utilizing asymmetric hydrogenation of *o*-bromo-*p*'-methylbenzophenone (**1f**) as a key step where in the bromine atom acts as an enantiodirective functional substituent (Table 2). Thus, the hydrogenation of a 0.8 M solution of **1f** in 2-propanol containing the Ru complex (*S,S*)-**4a** and *t*-C₄H₉OK (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*-C₄H₉Li 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, [α]_D²⁵ +8.65° (*c* 0.780, CHCl₃), in 96% yield.¹⁷ This chiral alcohol can readily be converted to (*R*)-**8**.¹⁹

(16) For catalytic asymmetric addition of Ti(C₆H₅)(OCH(CH₃)₂)₃ or Zn(C₆H₅)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.

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(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*-C₄H₉OK 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; [α]_D²⁰ –21.51° (*c* 1.13, CHCl₃).¹⁷

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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

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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