Practical Enantioselective Hydrogenation of Aromatic Ketones

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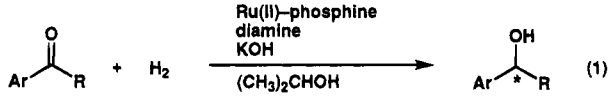
Enantioselective hydrogenation of prochiral ketones to optically active secondary alcohols is among the most fundamental subjects in modern synthetic chemistry.[1] BINAP–Ru(II) complex catalysts [BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (**1**)] have proved extremely efficient for the asymmetric hydrogenation of functionalized ketones,[1,2] which results in the industrial production of synthetic intermediates of antibiotic carbapenems[2e,3] and antibacterial Levofloxacin.[4] Rate enhancement and stereochemical control are effectively accomplished by coordination of the functional group to the catalytic Ru center. BINAP–Ru catalysts, though displaying a very wide scope, are unable to hydrogenate simple ketones that lack heteroatoms anchoring the Ru metal. This paper discloses a new and very practical catalyst system that effects enantioselective hydrogenation of the simple aromatic ketones in eq 1. This asymmetric synthesis compares well with existing procedures for catalytic enantioselective reductions.[5–7]



Phosphine–Ru(II) complexes are normally not very active as catalysts for hydrogenation of acetophenone.[8] The activity of $RuCl_2[P(C_6H_5)_3]_3$ was remarkably enhanced with the addition of 1 equiv of ethylenediamine and a >2.8 mM solution of KOH in 2-propanol. The turnover frequency (TOF, defined as moles of the product per mole of the catalyst per hour) of the reduction with $RuCl_2[P(C_6H_5)_3]_3$ alone was less than 5, while the use of the present system led to a TOF of 6700 ([Ru] = 0.28 mM in 2-propanol, $Ru:NH_2(CH_2)_2NH_2:KOH$ = 1:1:20, substrate to catalyst (S/C) mole ratio = 5000, 3 atm of H_2, 28 °C). The rate is highly sensitive to the pressure of hydrogen. Thus, the initial TOFs attained at 1 atm (S/C = 500) and 50 atm (S/C = 10 000) were 880 and 23 000, respectively. This hydrogenation proceeds smoothly even at −20 °C. Both the organic and inorganic bases are required. Screening of the diamine ligands suggested that at least one primary amine end is necessary. KOH could be replaced by $(CH_3)_2CHOK$. 2-Propanol is the solvent of choice. The reaction in methanol, ethanol, or *tert*-butyl alcohol is much slower, while THF, dichloromethane, and toluene are not usable.

Although a transition metal complex–base combined system in 2-propanol has frequently been used for transfer hydrogenation of ketones,[7,9] this reductive transformation is a result of net hydrogenation. Under the above standard conditions, acetophenone absorbed H_2 smoothly to give 1-phenylethanol; in the absence of H_2, little alcoholic product was obtainable (TOF < 7). Interestingly, addition of ethylenediamine suppresses the nonhydrogenative reduction (TOF = 70) that occurs in 2-propanol containing $RuCl_2[P(C_6H_5)_3]_3$ and KOH. The absence of transfer hydrogenation was confirmed by the deuterium-labeled experiment. Thus, the Ru-catalyzed reaction in the presence of ethylenediamine and KOH in $(CH_3)_2CDOH$ (S/C = 500, 3 atm of H_2, 28 °C) gave only nondeuterated 1-phenylethanol in >99% yield. No acetone was formed. $(CH_3)_2CDOH$ was recovered without any change. The smooth reaction of benzophenone excluded the possibility of hydrogenation via an enol intermediate.

Encouraged by the marked activity of the new Ru catalyst system in hydrogenation of the simple ketonic substrate, we then examined the asymmetric version. The hydrogenation of 1′-acetonaphthone with a catalyst system consisting of $RuCl_2$-[(*S*)-binap](dmf)$_n$,[10] (*S,S*)-1,2-diphenylethylenediamine [(*S,S*)-**3**],[11] and KOH (1:1:2 mole ratio) in 2-propanol (S/C = 500, 4 atm of H_2, 28 °C, 6 h) afforded (*R*)-1-(1-naphthyl)ethanol in 97% ee and in >99% yield. The high degree of enantioface differentiation is a result of the synergetic effects of the chiral diphosphine and diamine. Replacement of the *S,S* diamine by the *R,R* enantiomer under otherwise identical conditions gave the *R* alcohol in only 14% ee. A combination of the (*S*)-BINAP–Ru complex and achiral ethylenediamine or achiral $RuCl_2[P(C_6H_5)_3]_3$ and (*S,S*)-**3** provided the *R* product in 57 and 75% ee, respectively.

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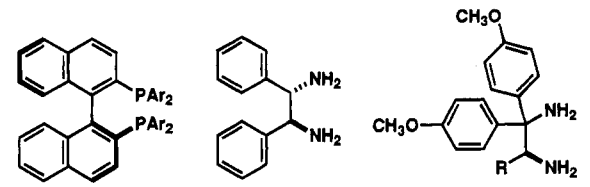
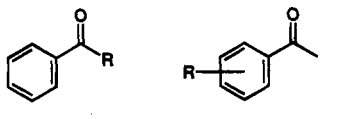


(S)-1: Ar ≡ C_6H_5 (BINAP)
(S)-2: Ar = p-$CH_3C_6H_4$ (TolBINAP)

(S,S)-3

(S)-4: R = CH_3
(S)-5: R = $(CH_3)_2CHCH_2$
(S)-6: R = $(CH_3)_2CH$



7a: R ≡ CH_3
7b: R = n-C_4H_9
7c: R ≡ $(CH_3)_2CH$
7d: R = $(CH_3)_3C$

8a: R = CH_3
8b: R = $(CH_3)_3C$
8c: R ≡ CH_3O
8d: R = Cl
8e: R = CH_3CO

A variety of aromatic ketones can be hydrogenated enantioselectively by the BINAP–Ru(II)–diamine–inorganic base combined catalyst system, where the diamines **3**–**6**[11,12] act as the most effective chiral controllers. Table 1 lists some representative examples. Hydrogen pressure does not affect the enantioselectivity. The extent of the enantioselectivity appears to be delicately influenced by the structures of the diamine auxiliaries as well as the substituents in the substrates. In general, use of (*S*)-BINAP and an *S* diamine affords the *R*-configurated alcohol product, whereas the *R*–*R* configurational combination gives the *S*-enriched alcohol. In the reaction of alkyl phenyl ketones **7**, the enantioselectivity was noticeably increased by increasing the bulkiness of the alkyl group from methyl to primary alkyls to isopropyl. Pivalophenone (**7d**), however, was far less reactive. Introduction of an alkyl, methoxy, or chloro substituent to the meta or para position of acetophenone tends to increase the degree of enantioselection. The ketones *m*-**8** and *p*-**8** are reduced with higher enantioselectivity than unsubstituted acetophenone (**7a**) irrespective of the electronic properties of the substituent. The hydrogenation of ortho-methylated and -chlorinated acetophenone, *o*-**8a** and *o*-**8d**, proceeded with a high stereoselectivity. The methoxy compound *o*-**8c** was unreactive, however. Both 1′- and 2′-acetonaphthone displayed an excellent enantioselectivity. The hydrogenation of α-tetralone gave the corresponding alcohol in 100% yield but in at most 59% ee. The application of the Horeau effect[13] allows the synthesis of chiral diols of a very high enantiomeric purity. Thus, while the hydrogenation of para-substituted acetophenone was achieved in 91–96% optical yield, the reaction of *p*-diacetylbenzene (**8e**) with the (*S*)-BINAP–Ru complex and *S* diamine (*S*)-**6** produced nearly enantiomerically pure (*R,R*)-*p*-bis(1-hydroxyethyl)benzene in 85% yield in addition to the meso diol in 15% yield. Notably, β-keto esters, the best substrates for the standard BINAP–Ru(II)-catalyzed hydrogenation,[1–4] are inert in the present reaction conditions.

In conclusion, a BINAP–Ru(II) complex–chiral diamine–KOH ternary system acts as a very practical catalyst for enantioselective hydrogenation of simple aromatic ketones. BINAP (**1**)[14] and chiral diamine **3**[11] are now commercially available, while the 1,2-diamines **4**–**6** and their analogues are readily obtainable from amino acids.[12] The reaction can be conducted easily on a preparative scale with an S/C ratio up to 5000 and a substrate concentration as high as 30% in 2-propanol.[15] The hydrogenation takes place smoothly at room temperature at 1–8 atm of H_2, while the reaction occurs very rapidly under high pressure. The workup procedure is simple; in most cases the product is obtainable by direct distillation of the reaction mixture.

Table 1. Enantioselective Hydrogenation of Aromatic Ketones Catalyzed by a BINAP–Ru(II) Complex–Chiral Diamine–KOH System[a]

ketone substrate[b]	chiral element: phosphine	chiral element: diamine	conditions: H_2, atm	conditions: time, h	alcohol product: % yield[c]	alcohol product: % ee[d]	alcohol product: config[e]
7a	(*S*)-**1**	(*S*)-**5**	4	3	>99	87	*R*
7b	(*S*)-**1**	(*S*)-**4**	4	3	>99	90	*R*
7c	(*S*)-**2**	(*S*)-**6**	8	6	>99	95[f]	*R*
o-**8a**	(*S*)-**2**	(*S,S*)-**3**	4	5	>99	94	*R*
o-**8d**	(*S*)-**2**	(*S,S*)-**3**	50	3	>99	94	*R*
m-**8c**	(*R*)-**1**	(*R*)-**6**	8	3	99	88	*S*
m-**8d**	(*S*)-**2**	(*S*)-**6**	8	1	96	90[g]	*R*
p-**8a**	(*R*)-**1**	(*R*)-**6**	4	3	>99	91	*S*
p-**8b**	(*S*)-**2**	(*S,S*)-**3**	4	1.5	>99	96[h]	*R*
p-**8c**	(*R*)-**1**	(*R*)-**6**	4	3	>99	92	*S*
p-**8d**	(*S*)-**2**	(*S*)-**6**	8	16	>99	94[i]	*R*
p-**8e**	(*S*)-**2**	(*S*)-**6**	4	1.5	98[j]	>99[k]	*R,R*
1′-NpCOCH$_3$	(*S*)-**1**	(*S,S*)-**3**	4	6	>99	97	*R*
1′-NpCOCH$_3$[l]	(*S*)-**1**	(*S,S*)-**3**	8	24	>99	95	*R*
2′-NpCOCH$_3$	(*S*)-**2**	(*S*)-**6**	1	18	99	95[m]	*R*
2′-NpCOCH$_3$	(*S*)-**2**	(*S*)-**6**	50[n]	3	98	97[m]	*R*

[a] Reaction was carried out at 11–30 °C using a 1.4 M solution of substrate (5.0 mmol) in 2-propanol. Substrate:Ru:diamine:KOH = 500:1:1:2. [b] Np = naphthyl. [c] Determined by GC and 200-MHz ^{1}H NMR analysis. [d] Determined by HPLC analysis using a DAICEL CHIRALCEL OB column (eluent, 10:90 2-propanol–hexane; flow rate, 0.5 mL/min) unless otherwise specified. [e] Determined by sign of rotation. [f] DAICEL CHIRALPAK AS column (3:97 2-propanol–hexane). [g] CHIRALCEL OJ column (5:95 2-propanol–hexane). [h] HPLC analysis of its acetate using a CHIRALPAK AS column (hexane). [i] A 3:97 2-propanol–hexane mixture as eluent. [j] *dl:meso* = 85:15. [k] HPLC analysis of its diacetate using a CHIRALPAK AS column (5:95 2-propanol–hexane). [l] A 30-g-scale reaction. For details, see footnote 15 and supplementary material. [m] CHIRALPAK AS column (5:95 2-propanol–hexane). [n] At −22 °C.

Supplementary Material Available: Full experimental procedure, $[\alpha]_D$ values of the reaction products, and analytical data (mp, $[\alpha]_D$, ^{1}H NMR, IR, and elemental analysis) of compound (*S*)-**5** (5 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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(15) Diamine (*S,S*)-**3** (7.5 mg, 0.035 mmol) and a 0.5 M 2-propanol solution of KOH (140 μL, 0.070 mmol) were added to 2-propanol (10 mL), and the mixture was degassed by freeze–thaw cycles. To this solution was added $RuCl_2$[(*S*)-binap](dmf)$_n$[10] (33.1 mg, 0.035 mmol), and the resulting mixture was sonicated for 10 min and used as a catalyst. A solution of 1′-acetonaphthone (30.0 g, 176 mmol) in 2-propanol (90 mL) was subjected to freeze–thaw cycles. These two solutions were transferred to a glass autoclave, and then, hydrogen was pressurized to 8 atm. The solution was vigorously stirred at 28 °C for 24 h. After the reaction, the solvent was removed under reduced pressure, and the residue was distilled to give (*R*)-1-(1-naphthyl)ethanol (27.90 g, 92% yield, 95% ee), bp 98–101 °C/0.5 mmHg, $[\alpha]^{23}_D$ +75.8° (*c* 0.99, ether) (lit.[16] $[\alpha]^{25}_D$ +82.1° (*c* 1.0, ether)). The yield determined by ^{1}H NMR was >99%.

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