Asymmetric Transfer Hydrogenation of Aromatic Ketones Catalyzed by Chiral Ruthenium(II) Complexes

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In response to an increasing demand for optically active secondary alcohols in the area of pharmaceuticals and advanced materials,¹ a series of asymmetric reductions of prochiral aromatic ketones has been developed.² In addition to straightforward asymmetric hydrogenation, sometimes catalytic reduction without using molecular hydrogen is also required. Evans³ found that the Meerwein-Ponndorf-Verley reduction of aryl methyl ketones catalyzed by a chiral amino alcohol-modified Sm(III) complex (substrate/catalyst (S/C) mole ratio = 20) proceeds smoothly at room temperature in a 2-propanol-THF mixture with >92% optical yield, although a higher catalytic efficiency would be preferable before putting the method to practical use. Certain chirally modified Rh(I),⁴ Ir(I),⁴ and Ru(II)⁵ complexes promote asymmetric reduction at high S/C ratios in refluxing 2-propanol. This method has been extensively studied because of the low cost and favorable properties of the hydrogen donor as well as the operational simplicity. However, the enantioselectivity has remained moderate. Here, we disclose a new type of chiral Ru(II) catalysts which effect a highly enantioselective reaction of aromatic ketones at room temperature (eq 1). This catalyst system is much more reactive than the previously reported aza-aromatic-,^{4a} phosphine-,^{5a-d} or imine-based^{5e} transition metal complexes.



Heating a mixture of $[RuCl_2(\eta^6-mesitylene)]_2^6$ and (1S,2S)-N-(p-toluenesulfonyl)-1,2-diphenylethylenediamine [(S,S)-Ts-DPEN, 1]⁷ (Ru atom: 1 mole ratio = 1:2) at 80 °C for 20 min under argon gave an orange solution, which can be used as a catalyst for transfer hydrogenation of aromatic ketones. Thus, when a 0.1 M solution of acetophenone (2a) in 2-propanol

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containing the in situ prepared Ru catalyst (S/C = 200) and KOH (5 equiv to Ru atom) was stirred at room temperature for 15 h. (S)-1-phenylethanol was obtained in 97% ee and 95% yield. Without TsDPEN under otherwise identical conditions, the alcoholic product was obtainable in <8% yield.



Since transfer hydrogenation of ketones is reversible, the overall efficiency is subtly influenced by the structures of the ketonic substrates and hydrogen donors as well as reaction conditions. The stereoselectivity of this reaction is obtained primarily by kinetic discrimination of enantiofaces of prochiral ketones, but the thermodynamic factors are not negligible. Thus, the reaction using a 1 M (not 0.1 M) solution of 2a in 2-propanol in the presence of the (S,S)-TsDPEN-based Ru catalyst gave at the start (S)- and (R)-1-phenylethanol in a ratio of 99:1. However, the selectivity decreased gradually as the reaction proceeded, and after 75% conversion, the enantiomer ratio was reduced to below 97:3. Comparison of the dehydrogenation rates between enantiomeric 1-phenylethanols revealed that the S alcohol is dehydrogenated ~ 2 orders of magnitude faster than the R enantiomer (eq 2). Thus, under the Ru-catalyzed

conditions, the prochiral ketone is converted enantioselectively to the S alcohol, but this enantiomer reverts back readily to the original ketone. An experiment as well as the thermodynamic data⁸ indicates that a 1-phenylethanol/acetophenone equilibrium ratio in a 1 M 2-propanol solution is \sim 80:20. Therefore, to obtain the chiral alcohol in a high yield without significant deterioration of the enantiomeric purity, the reaction is to be performed with a substrate concentration as low as 0.1 M, and an unnecessarily long exposure of the reaction mixture to the Ru catalyst should be avoided.

A variety of simple aryl alkyl ketones (S/C = 200-500) can be transformed to the corresponding secondary alcohols with high enantiomeric purity, as exemplified in Table 1. The rate and stereoselectivity are delicately affected by the bulkiness and electronic properties of the alkyl group and ring substituent. Acetophenone (2a) and propiophenone (2b) were reduced smoothly with >97% optical yield, but isobutyrophenone was not reduced at room temperature. Ortho-substituted acetophenones such as o-2c reacted slowly, as expected. Both 1'- and 2'-acetonaphthone are reduced with high enantioselectivity but at different rates. A p-methoxy group in acetophenone significantly decreases the enantioselectivity, whereas m-chloroacetophenone (m-2d) achieved the best result, 98% ee and 98%yield. The cyclic substrates 3 are also convertible to the corresponding alcohols with a high enantiomeric purity and a moderate conversion.

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 Table 1.
 Enantioselective Transfer Hydrogenation of Aromatic

 Ketones in 2-Propanol Catalyzed by a Chiral Ru(II) Complex^a

			alcohol	
ketone	time, h	yield, ^b %	ee,° %	config ^d
2a	15	95	97°	S
2b	14	94	97	S
o-2c	24	53	91	S
m-2d	2.5	98	98 ^e	S
$m-2d^{f}$	8	98, 95 ^s	98 ^e	S
p-2d	19	95	93 ^e	S
m-2e	16	96	96	S
p-2e	20	53	72	S
3a	20	45	91	S
3b	27	65	97	S
l'-acetonaphthone	62	92	93	S
2'-acetonaphthone	16	93	98 ^h	S

^{*a*} The reaction was carried out at room temperature using a 0.1 M solution of a ketone (5.0 mmol) in 2-propanol. Ketone:Ru:(*S*,*S*)-TsDPEN:KOH = 200:1:2:5. ^{*b*} Yield was determined by GLC or 400-MHz ¹H NMR analysis. ^{*c*} 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. ^{*d*} Determined from the sign of rotation of the isolated product. ^{*e*} Determined by capillary GLC analysis using a chiral Chrompack CP-cyclodextrin- β -236-M-19 column. ^{*f*} Result of a 20-mmol scale reaction with S/C = 500.¹² ^{*s*} Isolated yield. ^{*h*} Chiralpak AS column (5:95 2-propanol-hexane).

Screening of the auxiliaries of the Ru catalysts indicated that the rate and enantioselectivity of the reaction are highly influenced by the nature of the aromatic and nitrogen-based ligands. The reactivity of the [RuCl₂(η^{6} -benzene)]₂/N-substituted (1*S*,2*S*)-1,2-diphenylethylenediamine catalyst system tends to decrease with increasing electron-withdrawing ability of the nitrogen substituents, namely, in the order of C₆H₅CO > *p*-CH₃-OC₆H₄SO₂ > C₆H₅SO₂ > CF₃SO₂, while the sulfonylated compounds give a higher enantioselectivity. At the present time, the combined use of mesitylene and TsDPEN provides the best result for the asymmetric transfer hydrogenation of aromatic ketones.

Although the nature of the real catalyst remains unknown, a relevant crystalline Ru(II) complex that acts as catalyst precursor could be isolated from a 1:4 mixture of $[RuCl_2(\eta^6\text{-benzene})]_2$ and (1S,2S)-N-(trifluoromethanesulfonyl)-1,2-diphenylethylene-diamine [(S,S)-TfDPEN] in 2-propanol. The molecular structure determined by single-crystal X-ray analysis is shown in Figure 1. The (R)-Ru(II) center⁹ possesses a chloride, an η^6 -benzene ligand, and a five-membered chelate ligand with a neutral amino and anionic amido moiety.¹⁰ This preformed mononuclear Ru complex reduces **2a** in 2-propanol containing KOH to give (S)-1-phenylethanol at a comparable rate and with the same enantioselectivity in comparison to the *in situ* generated catalyst (for example, 8% yield and 90% ee vs 11% yield and 90% ee after 1 h-reaction in a 1 M solution).¹¹

This catalytic reaction represents a substantial improvement



Figure 1. ORTEP plot (50% probability ellipsoids) of the molecular structure of (*R*)-RuCl[(15,25)-*N*-(SO₂CF₃)NCH(C₆H₅)CH(C₆H₅)NH₂]-(η^{6} -benzene). Selected bond lengths (Å): Ru(1)-Cl(1), 2.463(3); Ru(1)-N(1), 2.139(6); Ru(1)-N(2), 2.105(6); N(1)-C(1), 1.527(8); N(2)-C(2), 1.486(10). Selected bond angles (deg): Ru(1)-N(1)-S(1), 120.7(3); Ru(1)-N(1)-C(1), 112.7(4); Ru(1)-N(2)-C(2), 113.2(5); S(1)-N(1)-C(1), 118.0(5); Cl(1)-Ru(1)-N(1), 86.0(2); Cl(1)-Ru(1)-N(2), 82.2(2); N(1)-Ru(1)-N(2), 78.7(2).

over the earlier systems.^{3-5,12} Although the overall catalytic performance is unable to rival that of the current best hydrogenation method,^{2c} this result provides a useful index for designing further efficient catalyst systems.

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Supporting Information Available: $[\alpha]_D$ values of the reaction products, experimental procedure for transfer hydrogenation of *m*-2d (20 mmol, S/C = 500), and data of single-crystal X-ray analysis of (*R*)-RuCl[(*S*,*S*)-TfDPEN](η^6 -benzene) (19 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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⁽¹¹⁾ The TfDPEN-based catalyst is about one-third as reactive as the TsDPEN analogue.

⁽¹²⁾ A procedure for the reaction using 20 mmol of m-2d (S/C = 500) is given in the supporting information.