Ruthenium(II)-Catalyzed Asymmetric Transfer Hydrogenation of Ketones Using a Formic Acid−Triethylamine Mixture

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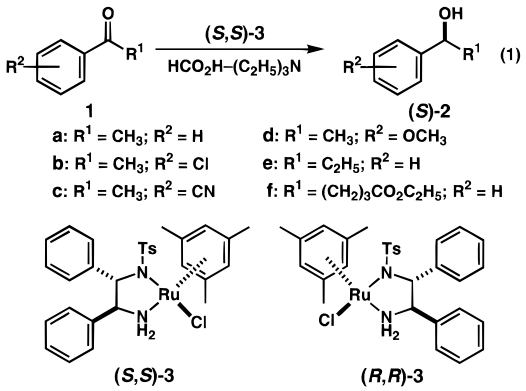
Catalytic transfer hydrogenation of ketones to alcohols with 2-propanol sometimes offers an attractive alternative to the reaction with molecular hydrogen because of the favorable properties of the organic hydrogen source.[1] However, when the method is applied to the asymmetric version,[2−4] it encounters inherent chemical problems. Even if the reduction proceeds with excellent kinetic enantioface discrimination, the occurrence of the reverse process originating from the structural similarity of the hydrogen donor and product, both being secondary alcohols, frequently deteriorates the enantiomeric purity of the chiral product.[1−5] In addition, the unfavorable ketone:alcohol equilibrium ratio often prevents a high conversion. Use of formic acid[6] in place of 2-propanol presents an obvious possibility to solve these problems. This hydrogen donor, viewed as an adduct of H_2 and CO_2, must effect the reaction irreversibly with truly kinetic enantioselection and, in principle, 100% conversion. However, its use in asymmetric ketone reduction has remained elusive because of the lack of suitable transition metal catalysts.[7] We have found that Ru(II) complexes modified with an arene and a chiral *N*-tosylated 1,2-diamine[2] serve as efficient catalysts for the asymmetric reduction using a 5:2 formic acid−triethylamine azeotropic mixture under mild conditions.

The reduction of acetophenone (**1a**) to 1-phenylethanol (**2a**) was selected as the model reaction (eq 1: $R^1 = CH_3$; $R^2 = H$). Screening experiments revealed that the catalyst of choice was the chiral Ru complex, (*R*)-RuCl[(1*S*,2*S*)-*p*-TsNCH(C_6H_5)CH(C_6H_5)NH_2](η^6-mesitylene) [(*S*,*S*)-**3**] or the enantiomer [(*R*,*R*)-**3**], which was prepared by reacting [$RuCl_2$(η^6-mesitylene)]$_2$, (1*S*,2*S*)- or (1*R*,2*R*)-*N*-(*p*-tolylsulfonyl)-1,2-diphenylethylenediamine (TsDPEN), and triethylamine (Ru atom:TsDPEN:triethylamine molar ratio = 1:1:2) in 2-propanol at 80 °C for 1 h.[2,8] Reaction using a 2 M solution of **1a** in a 5:2 formic acid−triethylamine azeotrope[9] containing (*S*,*S*)-**3** [substrate/catalyst (S/C) mole ratio = 200:1, 28 °C, 20 h] gave (*S*)-**2a** in 98% ee and in >99% yield.[10] The reaction at 60 °C proceeded 8−10 times faster with a 2% decrease in ee. This reduction can be conducted even in a 10 M solution (ca. 50% v/v concentration) and with S/C = 1000:1. The reactivity and enantioface-differentiation ability of the Ru complex **3** result from the compromise between the steric and electronic properties of the arene ligand and the chiral diamine auxiliary. The reactivity decreases in the order benzene > *p*-cymene and mesitylene > hexamethylbenzene as ligand, while mesitylene or *p*-cymene displays a better enantioselection than unsubstituted benzene. The presence of the NH_2 terminus in the TsDPEN auxiliary is crucially important. The $NHCH_3$ analogue showed a comparable enantioselectivity but with much lower reactivity; the $N(CH_3)_2$ derivative gave very poor reactivity and stereoselectivity.



As shown in Table 1, a range of aromatic ketones can be reduced to the secondary alcohols with a high chemical yield and a satisfactory ee. Various acetophenone derivatives, **1b**−**d**, and the higher analogues, **1e** and **1f**, as well as acetonaphthones (**4** and **5**) can be used as substrates. The absence of the reverse process was confirmed by exposure of enantiomerically pure (*S*)- and (*R*)-**2a** to the reaction conditions with or without ketone **1b**. The irreversibility of the reaction results in a series of benefits. Enantioselectivity of the reduction using a 2 M solution of **1a** with (*S*,*S*)-**3** is kept consistently high (*S*:*R* = 99:1) throughout the reaction until completion. With a 2 M solution of **1a** in 2-propanol, the yield of (*S*)-**2a** cannot be high (at most 63%) for thermodynamic reasons, the calculated **2a**:**1a** equilibrium ratio being ca. 70:30.[2] Furthermore, the new reaction system reduced *p*-methoxyacetophenone (*p*-**1d**), among the most notorious substrates, to (*S*)-*p*-**2d** in 97% ee and >99% yield, presenting a significant improvement from the result in 2-propanol (70% ee and 33% yield after 6 h).

Although various para-substituted acetophenones are consistently convertible to the alcohols with >90% ee (Table 1), the

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(8) (*S*,*S*)-**3**: orange solid; mp 218.6−222.5 °C dec; ^{1}H NMR ($CDCl_3$) 2.24 (s, 3H, CH_3), 2.38 (s, 9H, CH_3), 3.69 (dd, 1H, J = 11.2 and 11.2 Hz, C*H*NH_2), 3.79 (d, 1H, J = 11.2 Hz, CHNTs), 3.99 (dd, 1H, J = 9.3 and 11.2 Hz, NH), 4.19 (brd, 1H, J = 9.3 Hz, NH), 5.30 (s, 3H, arom), 6.65−6.93 (m, 9H, arom), 7.06−7.15 (m, 3H, arom), 7.35 (d, 2H, J = 7.8 Hz, arom). Recrystallization from 99% ethanol afforded crystals of (*S*,*S*)-**3**·H_2O: mp 220.1−222.3 °C dec; ^{1}H NMR ($CDCl_3$) δ 1.58 (s, H_2O), 3.98−4.12 (br, 2H, NH_2). Chemical shifts of other signals were identical with those of (*S*,*S*)-**3**. The molecular structure determined by single-crystal X-ray analysis confirms the *R* configuration at the Ru center[2] (see supporting information).

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(10) The reaction can conveniently be conducted in an open vessel using a mixture of [$RuCl_2$(η^6-mesitylene)]$_2$ and TsDPEN in a formic acid−triethylamine mixture without isolating **3**.

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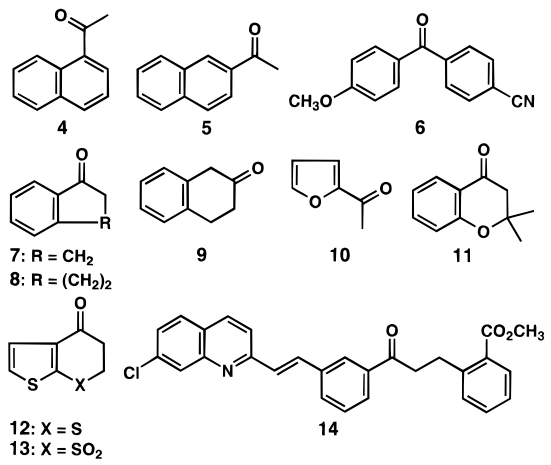
Table 1. Asymmetric Transfer Hydrogenation of Ketones in a Formic Acid−Triethylamine Mixture Catalyzed by a Chiral Ru(II) Complex[a]

			alcohol		
ketone	**3**, catalyst	time, h	% yield[b]	% ee[c]	config[d]
1a	*S,S*	20	>99	98[e]	*S*
1a	*S,S*	1.5[f]	>99	96[e]	*S*
1a[g]	*S,S*	60	>99	98[e]	*S*
m-**1b**	*S,S*	21	>99	97[e]	*S*
p-**1b**	*S,S*	24	>99	95[e]	*S*
p-**1c**	*S,S*	14	>99	90[h]	*S*
m-**1d**	*S,S*	50	>99	98	*S*
p-**1d**	*S,S*	60	>99	97	*S*
1e	*S,S*	60	96	97	*S*
1f	*S,S*	90	99	95[i]	*S*[j]
4	*S,S*	60	93	83	*S*
5	*S,S*	22	>99	96[k]	*S*
6[l]	*S,S*	60	54	66[k]	*S*[m]
7	*S,S*	48	>99	99	*S*
8	*S,S*	48	>99	99	*S*
8	*S,S*	6[f]	>99	98	*S*
9	*S,S*	80	70	82[n]	*S*
10	*S,S*	36	>99	98[e]	*S*
11[l]	*S,S*	40	47	97[k]	*S*
12	*R,R*	40	95[o]	99	*R*[p]
13[q]	*R,R*	65	95[r]	98	*R*
14[l,q]	*R,R*	72	68[s]	92[k]	*R*

[a] The reaction was carried out at 28 °C using a ketone (5.0 mmol) in a formic acid−triethylamine mixture (5:2, 2.5 mL) with S/C = 200. [b] Determined by GLC or 400-MHz ^{1}H NMR analysis. [c] HPLC analysis using a Daicel Chiralcel OB column unless otherwise specified. Details are described in the supporting information. [d] Determined by the sign of rotation of the isolated product. [e] Capillary GLC analysis using a chiral Chrompack CP-cyclodextrin-β-236-M-19 column. [f] Reaction at 60 °C. [g] Reaction using a 10 M solution of the ketone (25 mmol) in a formic acid−triethylamine mixture (2:1, 2.7 mL, 25 mmol) with S/C = 1000. After 12 h, the reducing agent (0.4 mL, 10 mmol) was renewed. [h] Chiralcel OJ column. [i] Chiralcel OD column. [j] Determined after conversion to (*S*)-6-phenyltetrahydro-2*H*-pyran-2-one. [k] Chiralpak AS column. [l] THF (1 mL) was added to dissolve the ketonic substrate. [m] Determined by X-ray analysis after condensation with (*R*)-1-(1-naphthyl)ethyl isocyanate. [n] Chiralpak AD column. [o] (*R*)-5,6-Dihydro-4*H*-thieno[2,3-*b*]thiopyran-4-ol. [p] Determined after oxidation to the sulfone. [q] Reaction using 1.0 mmol of ketone in 0.5 mL of a 5:2 formic acid−triethylamine mixture. [r] (*R*)-5,6-Dihydro-4*H*-thieno[2,3-*b*]thiopyran-4-ol 7,7-dioxide. [s] (*R,E*)-Methyl 2-[3-[3-[2-(7-chloro-2-quinolinyl)ethenyl]phenyl]-3-hydroxypropyl]benzoate.



electron-withdrawing substituents tend to slightly decrease the enantioselectivity. A benzophenone derivative **6**, with electron-accepting and -donating substituents at the para positions, was reduced to (*S*)-*p*-methoxy-*p*′-cyanobenzhydrol in 66% ee,[11] a notable enantiomeric bias corresponding to $\Delta\Delta G^{\ddagger}$= 0.95 kcal/mol. The absolute configuration of the major enantiomer was determined by X-ray crystallographic analysis after condensation with (*R*)-1-(1-naphthyl)ethyl isocyanate. Thus, the enantiomeric bias of the asymmetric reduction appears to be generated by both steric and electronic factors.

Asymmetric reduction of 1-indanone (**7**) and 1-tetralone (**8**) is now best effected by this method to give 1-indanol and 1-tetralol in 99% ee and >99% yield. Furthermore, the 2-furyl ketone **10** and oxacyclic ketone **11** were reduced to the corresponding alcohol[12] with a high ee. The reaction of the sulfur-containing ketones **12** and **13** in the presence of (*R,R*)-**3** led to the *R* alcohols in >98% ee, which serve as key intermediates for the synthesis of MK-0417, an excellent carbonic anhydrase inhibitor.[13]

This transfer hydrogenation is selective for a keto function.[7] The reduction of the multifunctionalized ketone **14** catalyzed by (*R,R*)-**3** gave the desired *R* benzylic alcohol, an intermediate in the synthesis of L-699,392 (LTD_4 antagonist),[14] in 92% ee without affecting the olefinic bond, halogen atom, quinoline ring, and ester function.

Under the catalytic conditions, formic acid decomposes into H_2 and CO_2 to a substantial extent. However, gaseous hydrogen participates little in the alcohol formation. First, an attempted reaction of **1a** with hydrogen gas in a 2:1 mixture of acetic acid (a nonreducing formic acid analogue) and triethylamine under otherwise identical conditions (20 atm, [**1a**] = 2 M, S/C = 200, 28 °C, 20 h) gave (*S*)-**2a** in only 75% ee and 5% yield. The presence of formic acid (10 equiv with respect to Ru) did not show any marked effect. Furthermore, reaction of **1a** with a 5:2 formic acid−triethylamine mixture under a D_2 atmosphere (65 atm, HCO_2H:D_2 mole ratio = 1:29, S/C = 200, 28 °C, 40 h) formed (*S*)-**2a** in 98% ee and 99% yield, in which 0.08D and 0.18D (0.06D/hydrogen) were incorporated at the C(1) and C(2) positions (^{2}H NMR analysis).

In summary, this work presents the first successful use of a formic acid−triethylamine mixture for asymmetric transfer hydrogenation of ketones. This method overwhelms the energetic requirement of the reduction process, where an unfavorable thermodynamic balance is expected with 2-propanol as the hydrogen source. Thus, the asymmetric reaction proceeds under truly kinetic control to completion with a much higher substrate concentration (2−10 M) than in 2-propanol (<0.1 M).

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Supporting Information Available: Experimental procedures for the transfer hydrogenation, HPLC or GLC behavior, and $[\alpha]_D$ values of the products and data of single-crystal X-ray analysis of (*S,S*)-**3**·H_2O and (*S*)-(*p*-methoxyphenyl)(*p*′-cyanophenyl)methyl (*R*)-*N*-1-(1-naphthyl)ethylcarbamate (39 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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