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Stereoselective Synthesis of Optically Active α-Hydroxy Ketones and *anti*-1,2-Diols via Asymmetric Transfer Hydrogenation of Unsymmetrically Substituted 1,2-Diketones

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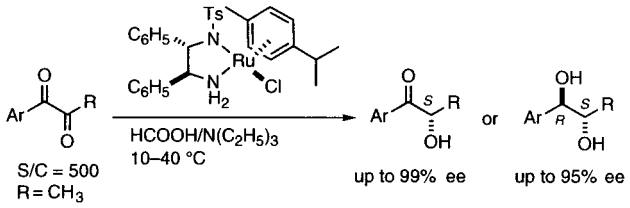
ABSTRACT



A well-defined chiral Ru catalyst RuCl(*N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine)(η^6-arene) effectively promotes asymmetric transfer hydrogenation of 1-aryl-1,2-propanedione with HCOOH/N(C_2H_5)$_3$, leading preferentially to optically active 1-aryl-2-hydroxy-1-propanone with up to 99% ee and 89% yield at 10 °C. The reaction at 40 °C gives *anti*-1-aryl-1,2-propanediol with up to 95% ee and 78% yield. This is a highly efficient procedure for the synthesis of optically active *anti*-diols.

Optically active α-hydroxy ketones are useful building blocks for the synthesis of biologically active compounds, natural products, and medicines, as well as chiral auxiliaries or ligands for asymmetric synthesis.[1] This important class of compounds has been prepared by means of oxidative[2−6] and nonoxidative[7,8] methods. Among these effective transformations, versatile methods include the enzymatic kinetic resolution of α-hydoxyketones[7] and the asymmetric oxidation of enolates or enol ethers using a stoichiometric amount of chiral *N*-sulfonyloxaziridines,[2] (salen)Mn catalysts,[3] or Sharpless dihydroxylation catalysts.[4]

Although the asymmetric catalytic reduction of readily available 1,2-diketones would be a promising approach, no practical reduction systems have been reported except for the enzymatic reduction systems[8] because there is a lack of suitable catalyst systems. Recently, we have developed a practical asymmetric synthesis of optically active diols via an asymmetric transfer hydrogenation of 1,2-diketones with a chiral Ru(II) catalyst, RuCl(Tsdpen)(η^6-arene)[9] (**1**; TsDPEN, *N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenedi-

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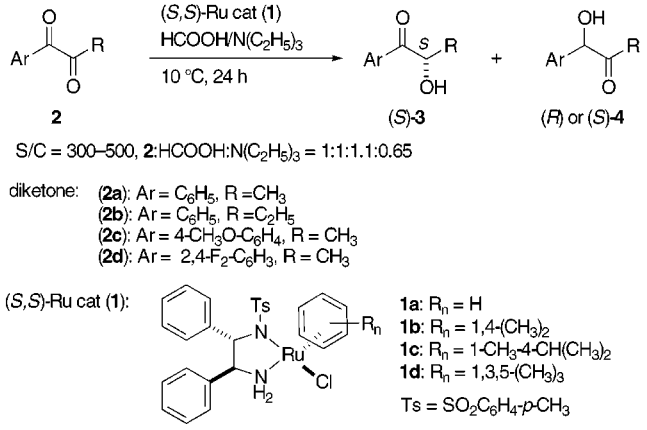
amine). In this synthesis, an efficient dynamic kinetic resolution of the α-hydoxy ketone intermediate, benzoin, led to the formation of optically active 1,2-diols in almost quantitative yields.[10] Here, we report the stereoselective synthesis of both optically active α-hydroxy ketones and *anti*-1,2-diols by this chiral Ru(II)-catalyzed asymmetric transfer hydrogenation of unsymmetrically substituted 1,2-diketones.

A well-defined chiral catalyst RuCl[(*S*,*S*)-Tsdpen](*p*-cymene) (**1c**) has proven to effect the asymmetric reduction of 1-phenyl-1,2-propanedione (**2a**) with a substrate/catalyst molar ratio (S/C) of 300 using 1 molar equiv of formic acid to **2a** (**2a**:HCOOH:$N(C_2H_5)_3$ = 1:1.1:0.65) at 10 °C, giving a 9:1 mixture of 1-phenyl-2-hydroxy-1-propanone, (*S*)-**3a**, with 99% ee and 1-phenyl-1-hydroxy-2-propanone, (*S*)-**4a**, with 12% ee with an overall yield of 99% (Scheme 1). Table 1 lists some representative examples.

Scheme 1



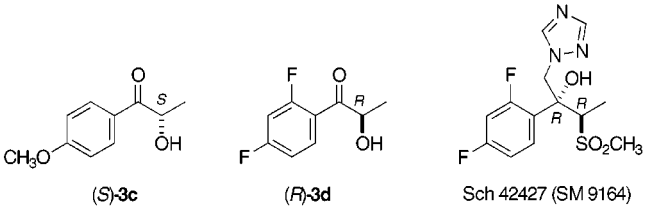
The reduction occurred at the less hindered carbonyl group in **2a**. A mixture of formic acid and triethylamine acts as both a hydrogen source and a reaction medium to attain excellent catalyst performance compared with the results attained in other organic solvents (Table 1). At higher temperatures, the enantioselectivity and regioselectivity significantly decreased. The stereochemical outcomes are also delicately influenced by the structures of the Ru complex as well as the thermodynamic and kinetic parameters of the ketonic substrates, although **4a** formation is thermodynamically favorable compared with **3a**.[11] The TsCYDN-based Ru complex RuCl[(*S*,*S*)-Tscydn](*p*-cymene) (**1e**; (*S*,*S*)-TsCYDN, (1*S*,2*S*)-*N*-(*p*-toluenesulfonyl)-1,2-cyclohexanediamine) exhibited stereoselectivity similar to that attained with **1c** albeit with somewhat lower reactivity. The molar ratio of products **3a** to **4a** depended on the choice of arene ligand on the catalyst, decreasing in the order of *p*-cymene > *p*-xylene > mesitylene > benzene. The *p*-cymene and *p*-xylene complexes displayed excellent enantioselection in the formation of **3a**.

In a similar manner, the asymmetric reduction of 1-phenyl-1,2-butanedione **2b** under otherwise identical conditions gave a mixture of **3b** with 95% ee and **4b** with 60% ee in an almost 1:1 ratio and 60% yield. The marked decrease in the regioselectivity can possibly be attributed to steric factors. Noticeably, diketone **2c**, bearing an electron-donating methoxy group at the para position on the phenyl group, was exclusively converted to (*S*)-1-(4′-methoxyphenyl)-2-hydroxy-1-propanone **3c** with 92% ee in 87% yield because of the decrease in the reactivity of the benzoyl group compared with that in unsubstituted **2a**. However, diketone **2d** with electron-withdrawing fluoro atoms gave mainly **4d** with 47% ee in addition to **3d** with an excellent enantiomeric excess, >99% (**3d**:**4d** = 1:2.7 in 79% yield); compound **3d** is a key intermediate of the antifungal agent Sch 42427 (SM 9164).[1a]

Table 1. Asymmetric Transfer Hydrogenation of 1,2-Diketones to α-Hydroxyketones Catalyzed by Chiral Ru(II) Catalysts with Formic Acid[a]

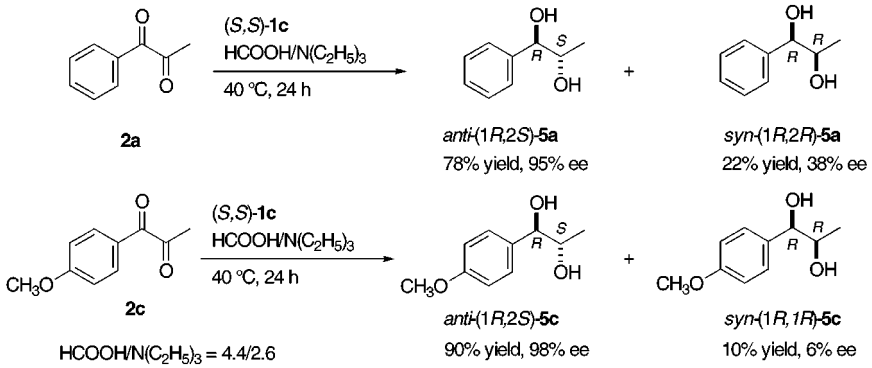
				product, **3** and **4**			
ketone	Ru catalyst	S/C	temp (°C)	yield (%)[b]	**3**:**4**[b]	ee (%)[c]	config[d]
2a	(*S*,*S*)-**1c**	300	10	99	89:11	99, 12	*S*,*S*
2a	(*S*,*S*)-**1c**	500	10	95	80:20	97, 6	*S*,*R*
2a	(*S*,*S*)-**1c**[e]	300	10	79	77:23	97, 12	*S*,*R*
2a	(*S*,*S*)-**1c**[f]	300	10	72	71:29	96, 21	*S*,*R*
2a	(*S*,*S*)-**1c**[g]	300	20	99	86:14	97, 49	*S*,*R*
2a	(*S*,*S*)-**1a**	500	10	95	51:49	87, 43	*S*,*R*
2a	(*S*,*S*)-**1b**	500	10	85	73:27	98, 36	*S*,*R*
2a	(*S*,*S*)-**1d**	500	10	88	61:39	93, 50	*S*,*R*
2a	(*S*,*S*)-**1e**	500	10	99	84:16	97, 27	*S*,*S*
2a	(*S*,*S*)-**1c**	500	0	26	77:23	96, 67	*S*,*R*
2a	(*S*,*S*)-**1c**	500	30	87	71:29	82, 35	*S*,*R*
2a	(*S*,*S*)-**1c**	500	40	82	48:52	24, 29	*S*,*R*
2b	(*S*,*S*)-**1c**	500	10	60	57:43	95, 60	
2c	(*S*,*S*)-**1c**	500	10	87	100:0	92,[0]	*S*[i]
2d	(*S*,*S*)-**1c**[h]	200	30	79	27:73	>99, 47	*S*,*R*

[a] The reaction of 1,2-diphenyl-1,2-propanedione (0.84 mmol) was carried out with a diketone/HCOOH/$N(C_2H_5)_3$ molar ratio of 1/1.1/0.65 at 10 °C for 24 h, unless otherwise noted. [b] Yields and molar ratio of **3** to **4** were determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as a internal standard. [c] Determined by HPLC analysis using a Daicel Chiralcel OB column or GLC analysis using a Chirasil-DEX CB column (25 m). [d] Determined by GLC or HPLC analysis in comparison to the authentic sample. [e] 0.1 M in CH_3CN. [f] 0.1 M in CH_2Cl_2. [g] 0.1 M in DMSO. [h] Diketone/HCOOH/$N(C_2H_5)_3$ molar ratio = 1/4.4/2.6, 24 h, 0.1 M in CH_2Cl_2. [i] Determined from the sign of rotation of the isolated product.



The general sense of the enantioface discrimination of each carbonyl group in **2a** observed with (*S*,*S*)-**1c** in this asymmetric reduction is well compared with the results obtained in the reduction of acetophenone derivatives with the same catalyst, indicating that the adjacent carbonyl function does not play any significant role, as was observed in the

Scheme 2



asymmetric reduction of benzils[10] or acetyl pyridines.[11] Note that, as exemplified in Table 1, excellent levels of enantioselection were observed with formation of the alcohols **3**, but alcohols **4** had lower ee values possibly because of intrinsic properties of α-hydroxy carbonyl units. In fact, treatment of optically active (*R*)-**4a** (92% ee) in a mixture of HCOOH/$N(C_2H_5)_3$ without Ru catalyst at 40 °C resulted in a rapid racemization along with the formation of 12% of racemic **3a** after 24 h. Experimental results as well as thermodynamic data[12] show that the equilibrium ratio of **4a** to **3a** at 40 °C in CD_3CN is ca. 80:20.[13] On the other hand, optically active **3a** (89% ee) did racemize and isomerize to **4a** to some extent under identical conditions at 40 °C, although it did not change significantly at 10 °C.[14] Therefore, long exposure of the products in the HCOOH/$N(C_2H_5)_3$ mixture containing Ru catalyst at higher temperature should be avoided in order to obtain the optically active α-hydrokyketones with high enantiomeric purities.

Thanks to characteristic properties of these α-substituted hydroxy ketones under the reaction conditions, stereoselective formation of optically active 1,2-diols can be achieved. Transfer hydrogenation of (*S*)-**3a** (89% ee) with a HCOOH/$N(C_2H_5)_3$ = 3.1/2.6 catalyzed by (*S*,*S*)-**1c** at 40 °C led preferentially to *anti*-(1*R*,2*S*)-1-phenyl-1,2-propanediol, (1*R*,2*S*)-**5a**, with >99% ee in 82% yield together with *syn*-(1*R*,2*R*)-1-phenyl-1,2-propanediol, (1*R*,2*R*)-**5a**, with 45% ee in 18% yield. In a similar manner, (*R*)-**3a** was reduced to afford mainly *syn*-(1*R*,2*R*)-**5a** with 96% ee in 86% yield (Table 2). In contrast, the reaction of racemic **4a** with a configurationally labile stereogenic center under the conditions mentioned in Table 2 gave mainly *syn*-(1*R*,2*R*)-**5a** with 83% ee in 74% yield via the dynamic kinetic resolution of racemic **4a**.

Table 2. Asymmetric Transfer Hydrogenation of α-Hydroxyketones and 1,2-Diketones to 1,2-Diols Catalyzed by Chiral Ru(II) Complex with Formic Acid[a]

		product, *anti*- and *syn*-**5**[b]			
ketone	S/C	yield (%)	*anti*:*syn*	ee, (%)*anti*,*syn*	config[c], *anti*, *syn*
(*S*)-**3a**	200	100	82:18	>99, 45	(1*R*,2*S*) (1*R*,2*R*)
(*R*)-**3a**	200	100	14:86	64, 96	(1*R*,2*S*) (1*R*,2*R*)
rac- **4a**	500	91	19:81	74, 83	(1*R*,2*S*) (1*R*,2*R*)

[a] The reaction of 1,2-diphenyl-1,2-propanedione (1.5 mmol) was carried out with a Ru catalyst (*S*,*S*)-**1c**, ketone/HCOOH/$N(C_2H_5)_3$ molar ratio = 1/3.1/2.6 at 40 °C, unless otherwise noted. [b] Yield and a *anti*/*syn* molar ratio of **5** were determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as a internal standard, and the ee values were determined by GLC analysis using a Chirasil-DEX CB column (25 m) of the acetonide derivative of **5**. [c] Determined from the GLC analysis in comparison to the authentic samples.

Optically active 1,2-diols are readily accessible from the one-pot reaction of 1,2-diketones by using this practical asymmetric transfer hydrogenation method. The reaction of **2a** with a S/C molar ratio of 200 in a HCOOH/$N(C_2H_5)_3$ mixture (4.4/2.6) at 40 °C for 24 h gave *anti*-(1*R*,2*S*)-**5a** with 95% ee and in 78% yield together with *syn*-(1*R*,2*R*)-**5a** as a minor product as shown in Scheme 2. Optically active **5a** is generated mainly from the enantioselective reduction of the intermediate **3a** and partly from the minor intermediate via a dynamic kinetic resolution (Scheme 3). Diketone **2c** bearing a methoxy group on the aromatic ring was reduced with high stereoselectivity to give *anti*-(1*R*,2*S*)-1-(4′-methoxyphenyl)-

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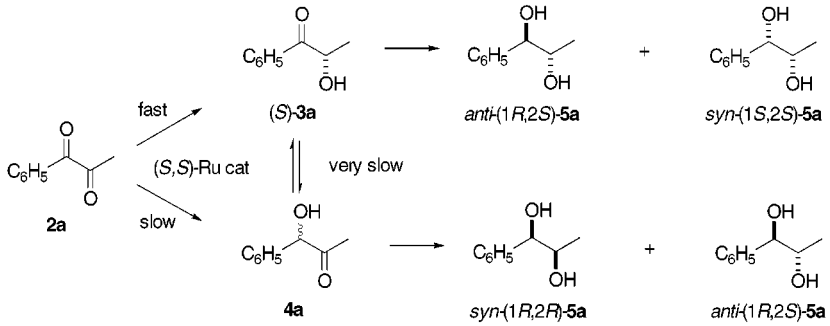
(13) The treatment of **3a** or **4a** in a mixture of HCOOH/$N(C_2H_5)_3$ (**3a** or **4a**:HCOOH/$N(C_2H_5)_3$ = 1:3.1:2.6, 0.1 M in CD_3CN) at 40 °C gave a 4:1 equilibrium mixture of **4a** and **3a** after 10 days.

(14) Treatment of (*R*)-**3a** with 89% ee with a mixture of HCOOH/$N(C_2H_5)_3$ (**3a**:HCOOH/$N(C_2H_5)_3$ = 1:3.1:2.6) at 40 °C for 24 h resulted in a racemization to 77% ee accompanied with a formation of 14% of **4a**. Reaction of (*R*)-**4a** under identical conditions resulted in a complete racemization with a formation of 12% of racemic **3a**.

Scheme 3



1,2-propanediol, *anti*-**5c**, which is a major metabolites of *trans*-anethole in the rat,[15] with 98% ee and in 90% yield.

This work presents the first successful reductive transformation of unsymmetrically substituted 1,2-diketones to optically active α-hydroxy ketone and *anti*-1,2-diols.[16] The reaction is characterized by high stereoselectivity in terms of regio-, diastereo-, and enantioselectivity. The coordinatively saturated nature of the Ru(II) complexes **1**, as well as the structural and electronic factors of the substrate, is responsible for the excellent stereoselective outcome of the asymmetric reduction.

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Supporting Information Available: Experimental procedure for the transfer hydrogenation reaction and analytical data for the reaction, This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) Although optically active *syn*-1,2-diols with extremely high ee's are readily accessible using the Sharpless AD reaction of *trans*-disubstitued olefins, *anti*-diols can be obtained with moderate to good ee's from the AD reaction of *cis*-olefins (*syn*-1-phenyl-1,2-propanediol **5b** with 97% ee vs *anti*-1-phenyl-1,2-propanediol **5a** with 72% ee). (a) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483−2547. (b) Kolb, H. C.; Sharpless, K. B. *Tetrahedron Lett.* **1992**, *50*, 10515−10530. (c) Wang, L.; Sharpless, K. B. *J. Am. Chem. Soc*. **1992**, *114*, 7568−7570.