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A Practical Stereoselective Synthesis of Chiral Hydrobenzoins via Asymmetric Transfer Hydrogenation of Benzils

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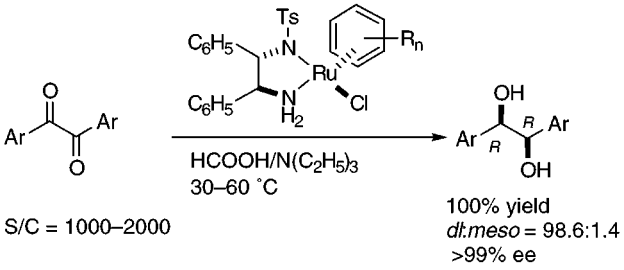
ABSTRACT



Asymmetric reduction of benzil with RuCl[(*S*,*S*)-Tsdpen)(η^6-*p*-cymene) in a mixture of formic acid and triethylamine proceeds with a substrate/catalyst molar ratio of 1000–2000 to give (*R*,*R*)-hydrobenzoin quantitatively with high diastereomeric (97% de) and enantiomeric purities (>99% ee), in which the benzoin intermediate with a chirally labile stereogenic center is converted to one major stereoisomer, (*R*,*R*)-product, via dynamic kinetic resolution.

Chiral 1,2-diols, especially, hydrobenzoins are useful building blocks for the syntheses of various biologically active compounds as well as chiral ligands and auxiliaries in stereoselective organic syntheses.[1] These important chiral hydrobenzoins have been prepared by resolution of racemic hydrobenzoins,[2] by stereoselective pinacol coupling of (η^6-*o*-substituted benzaldehyde)$Cr(CO)_3$ with samallium iodide,[3] and by Sharpless asymmetric dihydroxylation of *trans*-stilbene.[1a,4,5] Although asymmetric reduction of readily available α-diketones to chiral 1,2-diols would be a promising and widely applicable approach, no practical reduction systems have been reported except for oxazaborolidine-catalyzed reductions of benzils with borane/methyl sulfide,[6] which give chiral hydrobenzoins together with *meso*-1,2-

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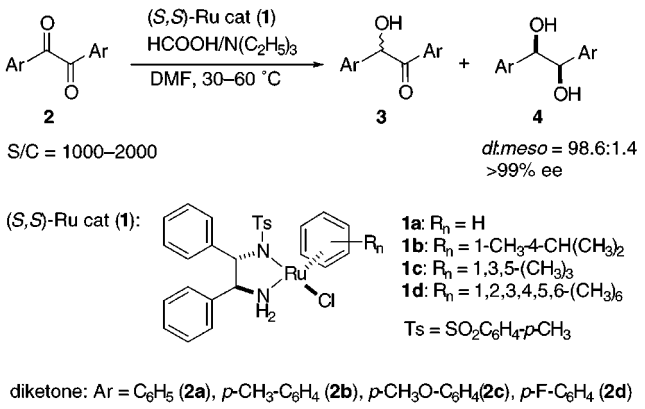
diols because of an inherent preference for the formation of the *meso*-isomers in the borane reduction. Chiral Ru-BINAP complexes effect the asymmetric hydrogenation of 1,2-diketones to give a mixture of chiral 1,2-diol with an excellent enantiomeric excess (ee) and *meso*-isomer. However, *meso*-isomer is the major product because the substrate control in the second hydrogenation step of the hydroxy ketone intermediate favors *meso*-diol formation.[7,8] Here, we describe the first practical asymmetric reduction of 1,2-diketones to chiral 1,2-diols catalyzed by well-defined chiral Ru(II) catalysts, RuCl(Tsdpen)(η^6-arene) (**1**) (TsDPEN, *N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine)[9] with the formic acid/triethylamine mixture as a hydrogen source.[10]

Asymmetric reduction of benzil (**2a**) catalyzed by the chiral Ru complex (*S,S*)-**1b** proceeds homogeneously at 40 °C with a substrate:catalyst molar ratio (S/C) of 1000 in a DMF solution of HCOOH/N(C_2H_5)$_3$ (benzil:HCOOH:N(C_2H_5)$_3$ molar ratio = 1:4.4:2.6, 0.95 M) to give almost quantitatively chiral (*R,R*)-hydrobenzoin (**4a**) with excellent diastereomeric (*dl*:*meso* = 98.6:1.4) and enantiomeric purities (>99% ee) (Scheme 1). The *p*-cymene and mesitylene

Scheme 1



complexes **1b** and **1c** effected the reaction equally well, while the benzene complex **1a** was more reactive but less selective. The hexamethylbenzene complex **1d** showed extremely high stereoselectivity although less reactivity at 40 °C. However, when the temperature was increased to 60 °C, the yield went from 5% to 22% without a significant loss in the selectivity. RuCl(Tscydn)(η^6-*p*-cymene) **1e** (TsCYDN, *N*-(*p*-toluenesulfonyl)-1,2-cyclohexanediamine) is also usable. Formic acid is the best hydrogen donor for this reduction. Attempted reduction using a 0.05 M solution of 2-propanol containing (*S,S*)-**1b** (S/C = 100, 30 °C, 24 h) gave (*S*)-benzoin with a 10% ee and 42% yield, but hydrobenzoin was not produced.[10]

DMF is used to maintain the homogeneity of the reaction mixture, but is not crucial for the catalysis to be efficient and practical. In fact, the reaction of benzil with a S/C of 1000 (1.6 M) in a mixture of HCOOH and N(C_2H_5)$_3$ containing (*S,S*)-**1b** (**2a**:HCOOH:N(C_2H_5)$_3$ molar ratio = 1:4.4:2.6) proceeded heterogeneously at the early stages of the reaction because of the low solubility of **2a**. After 24 h at 40 °C, (*R,R*)-**4a** (*dl*:*meso* = 98.4:1.6, >99% ee) was formed stereoselectively in quantitative yields. Enantiomerically pure (*R,R*)-hydrobenzoin was obtained in 84% isolated yield by simple evaporation of triethylamine, washing with water, and crystallization from ethanol from a 10-g-scale reaction. In the absence of triethylamine, no conversion of benzils was observed. The addition of triethylamine to the reaction mixture resulted in a significant increase in the conversion of the benzils. A formic acid:triethylamine molar ratio of 4.4:2.6 to 4.4:4.4 gave the best catalyst performance in terms of reactivity and stereoselectivity.

Various benzil derivatives bearing substituents on aromatic rings were able to be stereoselectively reduced to the chiral hydrobenzoins with high ee's and in good yields. Table 1

Table 1. Asymmetric Transfer Hydrogenation of Benzils and Benzoin Catalyzed by Chiral Ru(II) Catalysts with Formic Acid[a]

Ru cat.	ketone	solvent	*t* (h)	yield (%)[b]	*dl*:*meso*[b]	ee (%)[c]	conf[d]
(*S,S*)-**1a**	**2a**	DMF	24	100	90.4:9.4	>99	*R,R*
(*S,S*)-**1b**	**2a**	DMF	24	97	98.6:1.4	>99	*R,R*
(*S,S*)-**1b**	**2a**	DMF	30	100	98.6:1.4	>99	*R,R*
(*S,S*)-**1c**	**2a**	DMF	24	96	98.1:1.9	>99	*R,R*
(*S,S*)-**1d**	**2a**	DMF	24	5	99.9:0.1	>99	*R,R*
(*S,S*)-**1d**[e]	**2a**	DMF	24	22	98.1:1.9	>99	*R,R*
(*S,S*)-**1e**	**2a**	DMF	24	47	93.8:6.2	>99	*R,R*
(*S,S*)-**1b**	**2a**	–	24	100	98.4:1.6	>99	*R,R*
(*S,S*)-**1b**[f]	**2a**	–	24	84	98.1:1.9	>99	*R,R*
(*S,S*)-**1b**[g]	**2a**	–	24	100(84)[h]	97.9:2.1	>99	*R,R*
(*R,R*)-**1b**	**2a**	–	24	100	98.0:2.0	>99	*S,S*
(*S,S*)-**1b**	**2b**	–	48	67	96.7:3.3	>99	*R,R*
(*S,S*)-**1b**[i]	**2c**	DMF	48	75	94.4:5.6	>99[j]	*R,R*
(*S,S*)-**1b**	**2d**	–	24	100	94.2:5.8	>99	*R,R*[k]
(*S,S*)-**1b**[l]	**3a**	DMF	24	100	98.2:1.8	>99	*R,R*

[a] The reaction of benzil (1.05 g, 5.0 mmol) was carried out with a S/C molar ratio of 1000, benzil:HCOOH:N(C_2H_5)$_3$ molar ratio = 1:4.4:2.6 in 0.95 M DMF solution at 40 °C, unless otherwise noted. [b] Yields and *dl*:*meso* ratios were determined by ^{1}H NMR. [c] Unless otherwise noted, determined by HPLC analysis using a Daicel Chiralcel OJ column. [d] Unless otherwise noted, determined from the sign of rotation of the isolated product. [e] At 60 °C. [f] Reaction with a S/C molar ratio of 2000. [g] Reaction of benzil (11.0 g, 52.3 mmol). [h] Isolated yield in parentheses. [i] The reaction was carried out with a S/C ratio of 200 and benzil:HCOOH:N(C_2H_5)$_3$ molar ratio = 1:4.4:4.4 in a 1.2 M DMF solution at 35 °C. [j] Determined by HPLC analysis using a Daicel Chiralcel OD column. [k] Determined by X-ray crystal structural analysis of the salt with (*S,S*)-1,2-diaminocyclohexane. [l] Racemic **3a**:HCOOH:N(C_2H_5)$_3$ molar ratio = 1:3.1:2.6 in a 1.2 M DMF solution.

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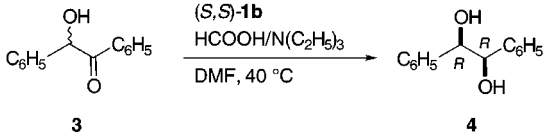
lists some examples. The benzils with electron-donating substituents (**2b** and **2c**) were reduced with excellent enantioselectivity but lower reactivity,[9] while the reduction of *p*-fluorobenzil (**2d**) proceeded rapidly as expected, giving a product with a high ee.

The success of the asymmetric reduction of benzils with the formic acid and triethylamine mixture relies strongly on the nature of benzoins **3** with a configurationally labile stereogenic center and the chiral structure and mechanism-based functional group discrimination ability of the chiral Ru complexes. Thanks to a sufficiently rapid stereomutation of **3** under the reaction conditions, the dynamic kinetic resolution of benzoins allows the diastereo- and enantioselective synthesis of chiral hydrobenzoins **4**. Thus, the reaction of racemic benzoin **3a** with a S/C of 1000 in a mixture of formic acid and triethylamine containing (*S*,*S*)-**1b** (**1b**:HCOOH:$N(C_2H_5)_3$ molar ratio = 1:3.1:2.6) at 40 °C gave (*R*,*R*)-**4a** quantitatively (*dl*:*meso* = 98.2:1.8, >99% ee) after 24 h (Scheme 2, Table 1). The products contained the

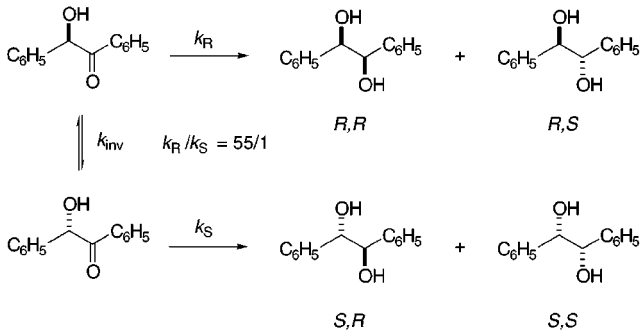
Scheme 2



3 **4**

same de and ee values as those attained at 4% conversion after 0.25 h. These results imply that the (*S*,*S*)-catalyst favors the reaction of (*R*)-benzoin. Computer-aided analysis of the reduction indicated that the rate of the reduction of (*R*)-benzoin with (*R*,*R*)-**1b** proceeds 55 times faster than the (*S*)-isomer.[11] The slow-reacting (*S*)-isomer undergoes a rapid racemization (Scheme 3).[12] Similarly, when racemic methyl

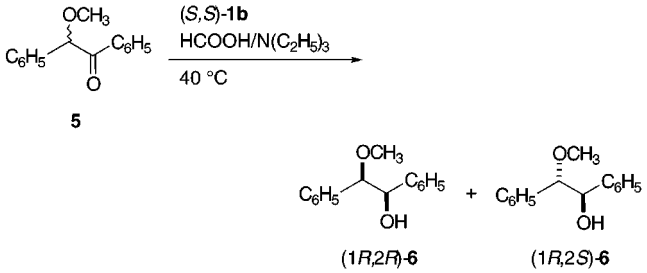
Scheme 3



ether **5** was reduced with the (*S*,*S*)-catalyst (**5**:HCOOH:$N(C_2H_5)_3$ molar ratio = 1:3.1:2.6, S/C = 1000) at 40 °C, for 24 h, a 92:8 mixture of the *syn* alcohol, (1*R*,2*R*)-**6** (98.0% ee) and the *anti* alcohol, (1*R*,2*S*)-**6** (57.4% ee) was obtained (Scheme 4).

In summary, this work presents the first asymmetric synthesis of enantiomerically pure hydrobenzoins via asym-

Scheme 4



5 (1*R*,2*R*)-**6** (1*R*,2*S*)-**6**

metric transfer hydrogenation of benzils or hydrobenzoins with formic acid as the hydrogen source. The coordinatively saturated nature of the diamine-based Ru(II)−arene complexes **1** with an excellent carbonyl group discrimination ability as well as structural factors of the substrate is responsible for the excellent stereoselective outcome of this reduction.[6,7,13,14] The CO_2 byproduct is potentially recyclable by using a rapid CO_2 hydrogenation method under supercritical CO_2 conditions.[15] Overall, the high rate of the reaction and operational simplicity attained here can make this reduction of readily available ketones practical. A 100-g-scale reduction of **2** or racemic **3** leads successfully to optically pure **4a** with an 80% isolated yield after one recrystallization from ethanol.

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Supporting Information Available: The $[\alpha]_D$ values of the reaction products and the experimental procedure for the transfer hydrogenation reaction of **2a** with Ru catalyst **1b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Asymmetric transfer hydrogenation of benzil by in situ generated diamine-based Ru catalyst using 2-propanol as a hydrogen source gave chiral hydrobenzoin with moderate enantiomeric purity (*dl*:*meso* = 31:69, 50% ee). Schwink, L.; Ireland, T.; Püntener, K.; Knochel, P. *Tetrahedron: Asymmetry* **1998**, *9*, 1143−1163.

(11) For computer-aided analysis of dynamic kinetic resolution, see: Noyori, R.; Tokunaga, M.; Kitamura, M. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 36−56 and references therein.

(12) The racemization strongly depends on the reaction conditions and the catalyst used. Future experiments will attempt to determine the mechanism of the interconversion of the enantiomeric **3**.

(13) Preliminary experiments showed that hydrogenation of **2a** catalyzed by a combined catalyst system of $RuCl_2$[(*R*)-binap][(*R*,*R*)-dpen] and KO-*t*-Bu gave racemic **3a** in 20% yield. No hydrobenzoin was obtained. Conditions: **2a**:Ru cat:KO-*t*-Bu molar ratio = 200:1:2.2, H_2 10 atm, 2-propanol/DMF = 5/1.5, 30 °C, 24 h. Two-component Ru catalyst, see: (a) Doucet, H.; Ohkuma, T.; Murata, K.; Yokozawa, T.; Kozawa, M.; Katayama, E.; England, A. F.; Ikariya, T.; Noyori, R. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1703−1707. (b) Ohkuma, T.; Koizumi, M.; Doucet, H.; Pham, T.; Kozawa, M.; Murata, K.; Katayama, E.; Yokozawa, T.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1998**, *120*, 13529−13530.

(14) Hydrogenation of **2a** catalyzed by Ru_2Cl_4[(*R*)-tolbinap]$_2$·($C_2H_5NH_2$) gave a mixture of benzoin in 3% yield and hydrobenzoin with *dl*:*meso* = 5:95 in 12% yield. Conditions: S/C = 200, H_2 40 atm, CH_3OH:CH_2Cl_2 = 5:1, 30 °C, 20 h. Ru−BINAP catalyst, see: Ikariya, T.; Ishii, Y.; Kawano, H.; Arai, T.; Saburi, M.; Yoshikawa, S.; Akutagawa, S. *J. Chem. Soc., Chem. Commun.* **1985**, 922−924.

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