Asymmetric Synthesis of Benzoin by SmI_2-Mediated Enantioselective Protonation

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Synopsis. Samarium (*Z*)-1,2-diphenylethen-1,2-diolate, which is considered to be an intermediate of a SmI_2-mediated reduction of benzil, was protonated enantioselectively by quinidine to afford (*R*)-benzoin in 91%ee. It was found that quenching the unreacted enediolate with oxygen was crucial to obtain high enantioselectivity. The configuration of the samarium enediolate was confirmed by isolating (*Z*)-*O*,*O*'-diacetyl-1,2-diphenylethen-1,2-diol.

The asymmetric reduction of benzil by a SmI_2-quinidine system reported by us[1] is the first example of a SmI_2-mediated enantioselective reaction. However, the enantioselectivity was low (56%ee) and the asymmetric reaction mechanism was not clear. Although the reaction was thought to proceed via an enantioselective protonation of samarium 1,2-diphenylethen-1,2-diolate, there was no evidence to confirm it. In this paper we describe attempts to achieve a higher enantioselectivity and to clarify the enantioselective reaction mechanism.

Results and Discussion

In order to find conditions for obtaining a higher enantioselectivity, the reaction time, amount of additive (HMPA), amount of quinidine (Q*) and reaction temperature were examined. The time course of the optical yield of the reaction (Table 1) indicates that the reduction of benzil by SmI_2 is accomplished within 35 s; the optical yield increases more slowly, reaching a maximum value after 30 min—1 h.

HMPA has been widely used as an additive to accelerate SmI_2-mediated reactions after being first used by Inanaga.[2] In our reaction, HMPA enhanced not only the reaction rate, but also the enantioselectivity.[3] The optical yield increased with increasing ratio of HMPA to SmI_2 (HMPA/SmI_2), reaching a maximum value at HMPA/SmI_2=1; it decreased when the ratio was larger than 1 (Fig. 1).

The optical yield also exhibited a maximum value (83%ee) at Q*/SmI_2=1.5, but decreased remarkably when the ratio became larger or smaller than that value (Fig. 2).

The enantioselectivity changed upon changing the ratio HMPA/Q*, but did not exceed 83%ee. Attempts to obtain a higher enantioselectivity by carring out the reaction at low temperature (−78—0 °C) were unsuccessful. The enantioselectivity was highest at room temperature.

As described initially, the intermediate of the enantioselective reaction is considered to be the samarium enediolate generated by a two-electron transfer from 2 equiv SmI_2 to benzil. If the enediolate is rather stable and protonation is incomplete, the unreacted enediolate affords racemic benzoin in quenching with 0.1 mol dm^{-3} hydrochloric acid, and the enantioselectivity should be lowered. Duhamel and Launay have reported that 1,2-diphenylethen-1,2-diol, which was formed by protonation of the corresponding potassium enediolate,

Table 1. Time Course of Chemical and Optical Yields of Benzoin[a]

Reaction time	Chemical yield/%[b]	%ee[b]
35 s	67 (90)	50 (38)
1 min	67	53
5 min	67 (82)	65 (64)
10 min	67	67
30 min	67 (82)	70 (69)
1 h	67	74
12 h	65	67
24 h	58	37

a) The reaction was carried out at room temperature at the ratio benzil:SmI_2:HMPA:Q*=1:2.7:2.3:3 and certain amount of sample was withdrawn from the reaction solution with syringe and quenched with 0.1 mol dm^{-3} hydrochloric acid under air. b) Determined by HPLC using chiral column: see Experimental section. The values in parenthesis are chemical yield and %ee when the reaction was carried out at the ratio benzil:SmI_2:HMPA:Q*=1:2.3:1.5:3.0 and quenched with 3.0 mol dm^{-3} deuteriochloric acid under argon.

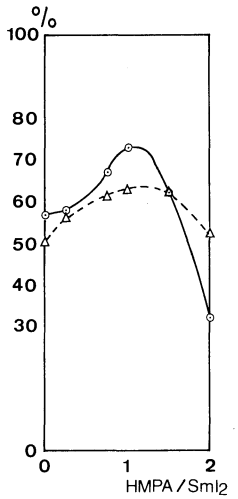


Fig. 1. Dependence of the optical and chemical yields of benzoin on HMPA/SmI_2 (The reaction was carried out at room temperature at the ratio benzil:SmI_2:Q*=1:2:2 and quenched with 0.1 mol dm^{-3} hydrochloric acid under air). —⊙—: Optical yield, - -△- -: chemical yield.

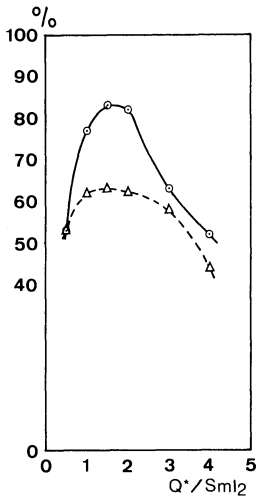


Fig. 2. Dependence of the optical and chemical yields of benzoin on Q*/SmI_2 (The reaction was carried out at room temperature at the ratio benzil : SmI_2 : HMPA= 1 : 2 : 2 and quenched with 0.1 mol dm^{-3} hydrochloric acid under air). —⊙—: Optical yield, --△--: chemical yield.

Table 2. Asymmetric Synthesis of Benzoin by SmI_2-Quinidine System Using O_2-Quenching Method[a)]

Entry	Reaction time	Chemical yield/%	%ee
1	10 s	36	85
2	30 s	48	91
3	30 min	61	91

a) The reaction was carried out at room temperature at the ratio benzil:SmI_2:HMPA:Q*=1:2.3:1.5:3.0. See Experimental section.

was oxidized to benzil by oxygen.[4)] We thus tried to oxidize the unreacted samarium enediolate by introducing oxygen into the reaction solution prior to quenching with 0.1 mol dm^{-3} hydrochloric acid. The enantioselectivity increased dramatically to 91%ee[5)] within 30 s, though the chemical yield of benzoin was lowered,[6)] as shown in Table 2.

This result strongly suggests the validity of an assumption that the samarium enediolate is an intermediate of the enantioselective reaction. In order to confirm this, we carried out deuteration and O_2-oxidation of the intermediate (Figs. 3 and 4, respectively).

As can be seen from Fig. 3, more than 80% of the intermediate is generated within 1 s and the amount reached 92% after 5 min. It is also evident from Fig. 4 that 95% of the intermediate was easily oxidized to benzil within 1 min: About 5% of benzoin may be formed before or during the oxidation process by O_2. Moreover, when the intermediate was reacted with an excess amount of acetic anhydride, and then quenched with 3 mol dm^{-3} deuteriochloric acid, (*Z*)-*O,O'*-diacetyl-1,2-diphenylethen-1,2-diol (**1**, 75%) and non-deuterated benzoin acetate (**3**, 17%) were isolated.[7)] (*E*)-*O,O'*-diacetyl-1,2-diphenylethen-1,2-diol (**2**) was not detected in the products by ^1H NMR analysis.

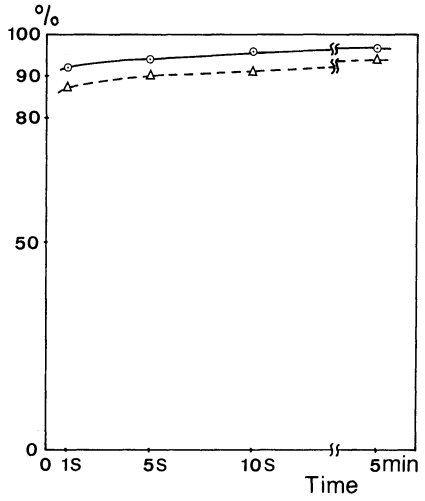


Fig. 3. Deuteration of the intermediate. —⊙—: The ratio of deuterated benzoin to the total amount of deuterated and non-deuterated benzoin, --△--: chemical yield of benzoin.

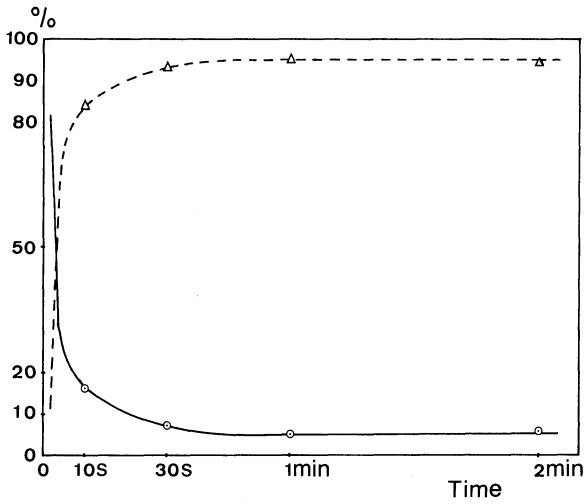
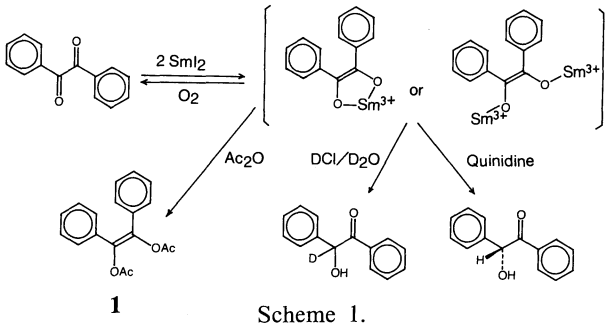


Fig. 4. O_2-oxidation of the intermediate (after addition of a SmI_2 solution and stirring for 10 s, oxygen was bubbled into the reaction solution: see Experimental section). —⊙—: Chemical yield of benzoin, --△--: the ratio of benzil to the total amount of the product.



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Scheme 1.

It is consequently clear that samarium (*Z*)-1,2-diphenylethen-1,2-diolate is the intermediate of SmI_2-

mediated enantioselective protonation. Quinidine and HMPA are considered to coordinate with the samarium enediolate to form a transient complex in which enantioselective protonation proceeds smoothly. Since the samarium enediolate has a C_{2v}-symmetric structure, (*R*)-enantiomer is produced predominantly if quinidine recognizes the left-hand carbon atom (*si*-face) of the olefinic double bond of the enediolate shown in Scheme 1.

Experimental

Quinidine and benzil were recrystallized from benzene. Tetrahydrofuran was distilled prior to use from sodium benzophenone ketyl under argon. The melting points were determined using a Yanagimoto micro-melting point apparatus, and were uncorrected. The IR spectra were recorded on a Hitachi 260-10 spectrometer. The ^{1}H NMR spectra were obtained on a JEOL-FX 200 spectrometer. The optical rotations were measured with a Perkin–Elmer 241 polarimeter. The enantioselectivity was determined by HPLC using a chiral column (Chiralcel OD; Hexane : 2-propanol=9 : 1): the enantiomers of benzoin, benzil and trace amount (<1%) of benzyl phenyl ketone[8] were completely separated. These products were isolated by preparative TLC and identified by comparing their IR and ^{1}H NMR spectra with those of authentic samples. The configuration of benzoin was determined to be *R* by its optical rotation (optically pure (*R*)-benzoin: $[\alpha]_D$ −118.5° (*c* 1, acetone)).[9] The chemical yield of the products was determined by HPLC analysis using benzyl phenyl ketone as an internal standard; its peak area was corrected using HPLC data in both the absence and presence of the internal standard.

Asymmetric Synthesis of Benzoin by SmI_2-Quinidine System. For a typical procedure, Entry 3 in Table 2 is described as follows: To a solution of benzil (30.1 mg, 0.143 mmol), quinidine (140 mg, 0.432 mmol), and HMPA (38.3 mg, 0.214 mmol) in THF (2 cm^3) was added a THF solution of SmI_2 (0.1 mol dm^{-3}, 3.3 cm^3, 0.33 mmol) under argon with stirring. The stirring was continued for 30 min at room temperature and then oxygen was bubbled into the solution for 1 min. To the solution was added 0.1 mol dm^{-3} hydrochloric acid (2 cm^3), and the organic materials were extracted with ether. The ethereal solution was washed successively with 3 mol dm^{-3} hydrochloric acid (5 cm^3), sat. NaCl soln, 2% $Na_2S_2O_3$ soln, and sat. NaCl soln and then dried over anhydrous Na_2SO_4. The ethereal solution was filtered and the filtrate was analyzed by HPLC. The yield of benzoin was 61.0% and the enantioselectivity was 91.1%ee. The 0.1 and 3 mol dm^{-3} hydrochloric acid solution were combined, and then the solution was made basic by adding a sodium hydroxide solution. Precipitates were extracted with ether, and the ethereal solution was dried over anhydrous Na_2SO_4. The ethereal solution was concentrated in vacuo to give crystalline materials (101 mg, 72% recovery) whose ^{1}H NMR spectrum and optical rotation ($[\alpha]_D^{20}$ +253.5° (*c* 0.938, ethanol)) were identical with those of quinidine used ($[\alpha]_D^{19}$ +253.7° (*c* 0.995, ethanol)).

Deuteration of the Intermediate. The reaction conditions were the same as those described above, except that quinidine was not used and a SmI_2 solution was added as fast as possible (within 1 s). Stirring was continued for a certain period and then the reaction was quenched under argon by quick injection (within 1 s) of 3 mol dm^{-3} deuteriochloric acid (2 cm^3), which was stored under argon. After the usual work-up, the ethereal solution was analyzed by HPLC, and then concentrated to give crystalline materials, which were purified by preparative TLC. The deuterated ratio of the purified benzoin was determined from integrating the methine and hydroxyl proton signals in the ^{1}H NMR spectrum.

O_2-Oxidation of the Intermediate. The reaction coditions were the same as those used in the deuteration experiment. After adding a SmI_2 solution and stirring for 10 s, oxygen was bubbled for a certain period and quenched by quick injection (within 1 s) of 3 mol dm^{-3} hydrochloric acid (2 cm^3). After the usual work-up, the ethereal solution was analyzed by HPLC.

Acetylation of the Intermediate. To a solution of benzil (101.3 mg, 0.482 mmol) and HMPA (136.6 mg, 0.762 mmol) in THF (5 cm^3) was added a SmI_2 solution (11.0 cm^3, 1.10 mmol) under argon with stirring. Stirring was continued for 13 min before adding acetic anhydride (1.0 cm^3, 10 mmol) into the deep-red reaction solution. After 1.5 h, 3 mol dm^{-3} deuteriochloric acid (2 cm^3) was added under argon into a pale-yellow suspension. After the usual work-up, the crude product was separated by preparative TLC to give **1** (107.3 mg, 75%), **3** (20.6 mg, 17%), and 4-acetyloxybutyl iodide[10] (289.8 mg), which were characterized by comparing their ^{1}H NMR and IR spectra with those of authentic samples (**1** and **3**). In no fraction of the products was **2** detected by ^{1}H NMR analysis. Authentic samples were prepared by Fieser's[11] (**1** and **2**) and Coroson's[12] methods: **1** [mp 119—121.5°C (lit,[11] 118—119°C); IR (KBr) 1750 cm^{-1} (ester C=O); ^{1}H NMR ($CDCl_3$) δ=2.20 (6H, s, $OCOC\underline{H}_3$), 7.24 (10H, m, Ph)], **2** [mp 156—158.5°C (lit,[11] 154—156°C); IR (KBr) 1750 cm^{-1} (ester C=O); ^{1}H NMR ($CDCl_3$) δ=2.08 (6H, s, $OCOC\underline{H}_3$), 7.36 and 7.54 (10H, m, Ph)] and **3** [mp 82.0—83.5°C (lit,[12] 81.5—82.5°C); IR (KBr) 1725 cm^{-1} (ester C=O), 1685 cm^{-1} (ketone C=O); ^{1}H NMR ($CDCl_3$) δ=2.19 (3H, s, $OCOC\underline{H}_3$), 6.86 (1H, s, $PhC\underline{H}$–$OCOCH_3$), 7.40 and 7.93 (10H, m, Ph)].

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6) The chemical yield of benzoin was lowered by quenching the reaction under air, for example, in Table 1, Figs. 1 and 2, probably because of the oxidation of the unreacted samarium enediolate and/or enediol during work-up.

7) Duhamel also established the (*Z*)-configuration of potassium 1,2-diphenylethen-1,2-diolate by quenching with acetic anhydride. See Ref. 4.

8) Benzyl phenyl ketone was formed by the SmI_2-mediated reduction of benzoin: G. A. Molander and G. Hahn, *J. Org. Chem.*, **51**, 1135 (1986).

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