

Concentration and Temperature Dependency of Regio- and Stereoselectivity in a Photochemical [2 + 2] Cycloaddition Reaction (the Paternò–Büchi Reaction): Origin of the Hydroxy-Group Directivity

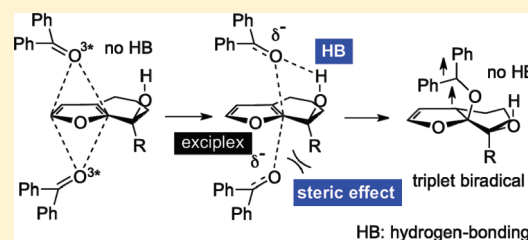
Youhei Yabuno,[†] Yoshikazu Hiraga,[†] Ryukichi Takagi,[†] and Manabu Abe^{*,†,‡}

[†]Department of Chemistry, Graduate School of Science, Hiroshima University (HIRODAI), 1-3-1 Kagamiyama, Higashi-Hiroshima, Hiroshima 739-8526, Japan, and

[‡]Japan Science and Technology Agency, CREST, 5 Sanbancho, Chiyodaku, Tokyo, 102-0075, Japan

S Supporting Information

ABSTRACT: A set of photochemical oxetane formation reactions, i.e., the Paternò–Büchi (PB) reactions, of tetrahydrobenzofuran derivatives **1a–d** with benzophenone (BP) was investigated to examine poorly understood hydroxy-group directivity on regio- and stereoselectivity. The selectivities of the PB reactions for allylic alcohols **1a,d** were found to be largely dependent upon the concentration of the allylic alcohols and the reaction temperature. The temperature-dependent change of the regioselectivity at high concentrations of allylic alcohols was similar to that of the hydroxy-protected methyl ether **1b** and tetrahydrobenzofuran (**1c**). The effect of concentration on regioselectivity can be explained by the hydrogen-bonded aggregates, which mimic the selectivities observed during the PB reaction of **1b,c**. The hydroxy-directed cis-selectivity of the higher-substituted oxetane **3a,d** formed at low concentration of **1a,d** was found to be larger than that at the higher concentration of **1a,d**. The cis-selectivity of **3a,d** was found to be higher than that of the lower-substituted oxetane **2a,d**. The regioselectivity of the cis-configured oxetanes was higher than that of the trans-configured oxetanes. These experimental results strongly suggest that hydroxy-group directivity, induced by hydrogen-bonding stabilization, plays a role in controlling the regio- and stereoselectivity of the PB reactions. The steric effect was also responsible for the diastereoselectivity, as shown by the fact that the cis selectivity in **3d** was higher than that in **3a**. Computational studies at the (U)MP2 and (U)DFT level of theory revealed that hydrogen-bonding stabilization becomes important only in the excited complex (exciplex) between the triplet excited state of carbonyls and alkenes, in which the charge transfer occurs from the alkene to the excited carbonyl to make the carbonyl oxygen nucleophilic. No significant stabilization energy was found in the intermediary triplet state of biradicals. The combined experimental and computational studies have clarified the origin of the poorly understood hydroxy-group effect on a high degree of regio- and stereoselectivity, i.e., the cooperative effect of hydrogen-bonding stabilization in exciplexes and the steric bulk of the substituents.



INTRODUCTION

The combined experimental and computational studies reported here were intended to reveal the origin of the poorly understood hydroxy-group directivity of regio- and diastereoselective [2 + 2] photocycloadditions [the Paternò–Büchi (PB) reactions]. The present study is a timely contribution to the current interest in the hydrogen-bonding interaction of open-shell molecules.¹

Hydrogen bonds have a significant influence on the structure of molecules/aggregates, on the function of materials, and on the selectivities of many chemical and biological systems.² The stabilization effects mediated by the hydrogen atom, i.e., hydrogen-bond energies, are largely affected by the acidity of donor groups and the basicity of acceptor groups. For the formation of a water or alcohol dimer, the enthalpy change of stabilization was found to be ca. 4–6 kcal mol^{−1}. Aggregation is an entropically

disfavored process. Thus, the temperature and the concentration of substrates, e.g. [ROH], largely affect the equilibrium constants, K_1 , K_2 , and K_3 , and the reactive species of monomers (k_1), dimers (k_2), and/or trimers (k_3) (Scheme 1). When the reaction partners, i.e., reagents, also have a potentially hydrogen-bonding nature, the binding constants also play a crucial role in the chemistry.

In organic synthesis, the energetic stabilization from hydrogen bonds in reaction intermediates and/or transition states is a well-known tool for the control of regioselectivity, chemoselectivity, diastereoselectivity, and enantioselectivity.³ In photochemical cycloaddition reactions, the structure of hydrogen-bonded complexes of two reacting compounds in the ground state was found to play crucial roles in controlling stereoselectivity, as exemplified in

Received: September 30, 2010

Published: February 9, 2011

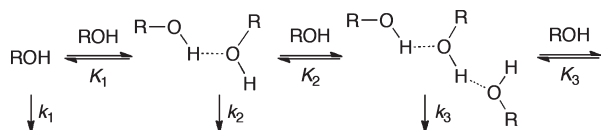
Scheme 2.⁴ The regio- and diastereoselectivity was found to increase in nonpolar solvents and at low temperature, under which conditions the entropically disfavored factor for the formation of the host–guest complex should be minimized. As for an intramolecular example, Snapper and co-workers reported a notable hydrogen-bonding effect on stereoselectivity in intramolecular [2 + 2] photocycloaddition reactions.⁵ In 2000, two research groups independently reported hydroxy-group-directed regio- and stereoselectivity during the formation of oxetanes in the Paternò–Büchi (PB) reaction⁶ of allylic alcohols with benzophenone (Scheme 3).⁷ Hydrogen-bonded stabilization in the excited states, i.e., the interaction of the n,π^* excited state of benzophenone (BP^{3*}) and alcohols, was proposed to play a role in controlling regio- and diastereoselectivity to afford the intermediary triplet 1,4-biradicals, followed by intersystem crossing (ISC) to stereoselectively produce oxetanes. A significant increase in diastereoselectivity was also found with an increase in the steric bulk of the substituent R and R' groups. The question then becomes how much energetic stabilization is expected to occur in the interaction between the excited state molecule (BP^{3*}), which possesses an excitation energy of $\sim 70 \text{ kcal mol}^{-1}$ and the lifetime of $\sim 7 \mu\text{s}$,⁸ and the hydroxyl group ($-\text{OH}$). The characteristics of an excited-state carbonyl can be seen in the resonance structures depicted in Scheme 3b.⁹ The oxygen atom of the n,π^* excited-state carbonyl possesses a radical characteristic¹⁰ and an electron deficiency,¹¹ which compares to that of a ground-state carbonyl.

In fact, Iwata and Morokuma reported that almost no stabilization energy was computed in the interaction of the n,π^* singlet/triplet state of formaldehyde with H_2O , although the stabilization energy of the hydrogen bond of ground-state formaldehyde (H_2CO) with H_2O was found to be ca. $3.5 \text{ kcal mol}^{-1}$.¹² The computational results are consistent with the well-known blue shift of the n,π^* transition of carbonyls.¹³ Thus, the transition in protic solvents needs more energy than that in aprotic solvents. The ground state stabilization retards the process of the n,π^* excitation of the carbonyl, which is necessary for the PB reaction. It is well-known that triplet state benzophenone abstracts a hydrogen atom from the CH group, rather than from the OH group, in the reaction with 2-propanol to give a ketyl radical.¹⁴ The hydrogen-bonded structure in the ground

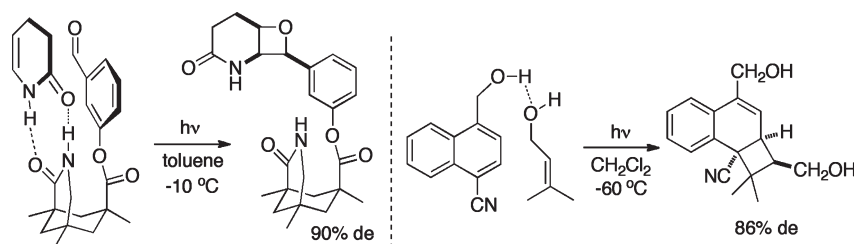
state should not cause the regio- and diastereoselectivity observed in the PB reactions. Thus, it is not clear whether the regio- and diastereoselectivity in the oxetane formation reaction is controlled by the hydrogen-bonding stabilization between the excited-state carbonyl and the hydroxyl group of the allylic alcohols. Griesbeck et al. have also pointed out a similar fundamental question concerning the hydroxyl-group directivity,¹⁵ but the origin of the directivity is still unclear. In recent reports, the stereoselectivity observed in the PB reaction of cyclic allylic alcohol, e.g., 2,3-dihydrofuran-3-ol, cannot be simply explained and predicted by the hydroxy-group directivity.¹⁶

As shown in Scheme 1, the concentration of substrates and the reaction temperature should mostly affect the reactive species, e.g., $k_1/k_2/k_3$, and thus, the product selectivity is expected to be significantly dependent on the reaction conditions. It is somewhat surprising that the effects of the reaction conditions have thus far not been examined for product selectivity in photochemical oxetane formations. In consideration of this background, we decided to conduct the PB reaction of BP with furan derivatives **1a,d** with the hydroxyl-group configurationally locked, thus giving clarification to the hydroxy group and its steric effect on product selectivity. First, the effects of concentration and temperature¹⁷ were thoroughly examined on regio- and stereoselectivity in the PB reaction of tetrahydrobenzofuranol derivative **1a** with the triplet n,π^* excited state benzophenone (BP^{3*}).¹⁸ Photocycloaddition reactions with **1b,c** were also done to clarify the role of the hydroxyl group on regio- and stereoselectivity in a photochemical reaction. The steric effect, which should be considered as one of the important factors in

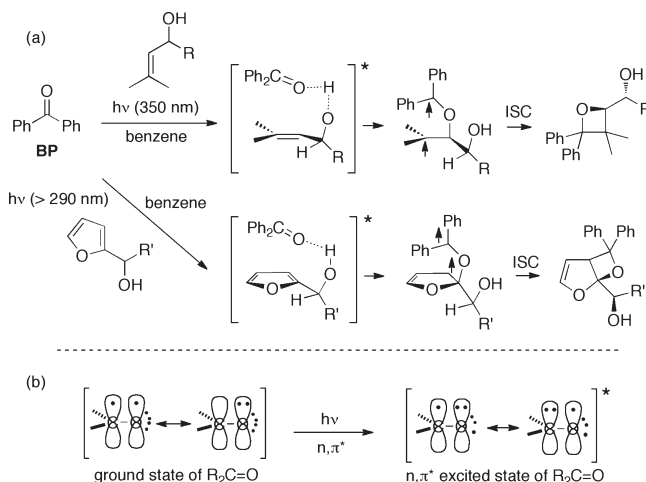
Scheme 1



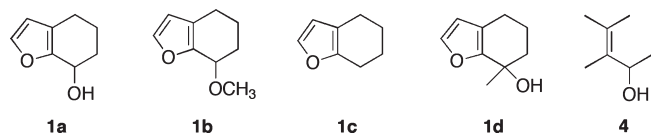
Scheme 2



Scheme 3



controlling selectivity, was examined in the PB reaction of **1d**. Computational studies have provided insight into the interaction of a hydroxyl group with a triplet n,π^* excited-state carbonyl during the formation of the intermediary triplet 1,4-diradicals and also have revealed the conformational stability of the intermediary triplet biradicals.¹⁹ Combined experimental and theoretical study has revealed that hydroxy-group selectivity in the PB reaction could be reasonably explained by the cooperative effect of hydrogen-bonded stabilization in the intermediary exciplex and by the steric bulk of substituents, leading to the preferred formation of oxetanes. Finally, the optimized conditions found in the present study were applied to improve the stereoselectivity of the PB reaction of allylic alcohol **4**.



EXPERIMENTAL METHODS

General Procedure for the Photoreactions of Benzophenone with Furan Derivatives. A dried and degassed toluene solution of freshly prepared furan derivative **1**²⁰ and benzophenone was irradiated for 6 h with a high-pressure Hg lamp through a Pyrex filter at various temperatures and concentrations. After the solvent was removed under reduced pressure using a vacuum pump (0.2 mmHg, <10 °C), the photolysate was directly analyzed by ¹H NMR (500 MHz) spectroscopy. The product yields were determined on the basis of the ¹H NMR (500 MHz) peak areas (error ±3%). Triphenylmethane (Ph₃CH) was used as an internal standard. The product ratios were determined by comparisons of the peak areas. The photoproducts were isolated using silica gel column chromatography. All of the configurational determinations, i.e., trans- and cis-configuration, were unequivocally determined by measuring the NOE enhancements in compounds **2a,b,d** and **3a,b,d**. This spectroscopic evidence is summarized in the Supporting Information.

(2aR*,6S*,7aR*)-2,2-Diphenyl-2a,3,4,5,6,7a-hexahydro-2H-oxeto[2,3-b]benzofuran-6-ol (trans-2a). ¹H NMR (500 MHz, CDCl₃): δ 0.88–1.01 (m, 1 H), 1.10–1.21 (m, 1 H), 1.45–1.82 (m, 4 H), 1.99–2.09 (m, 1 H), 4.37 (d, 1 H, *J* = 4.1 Hz), 4.39–4.47 (m, 1 H), 6.24 (d, 1 H, *J* = 4.1 Hz), 7.15–7.37 (m, 6 H), 7.38–7.51 (m, 4 H). ¹³C NMR (125 MHz, CDCl₃): δ 19.32 (CH₂), 22.94 (CH₂), 31.74 (CH₂), 58.58 (CH), 63.24 (CH), 94.52 (C), 104.94 (CH), 112.33 (C), 126.14 (CH), 126.35 (CH), 127.56 (CH), 127.75 (CH), 127.86 (CH), 128.55 (CH), 141.93 (C), 145.00 (C), 155.51 (C). Mp: 157 °C. HRMS (EI): calcd for C₂₁H₂₀O₃ 320.1413, found 320.1424. Anal. Calcd for C₂₁H₂₀O₃: C, 78.73; H, 6.29. Found: C, 78.72; H, 6.39. IR (KBr): 3529, 3023, 2991, 2948, 2893, 1955, 1699 cm⁻¹.

(2aS*,6S*,7aS*)-2,2-Diphenyl-2a,3,4,5,6,7a-hexahydro-2H-oxeto[2,3-b]benzofuran-6-ol (cis-2a). ¹H NMR (500 MHz, CDCl₃): δ 0.84–0.95 (m, 1 H), 1.04–1.21 (m, 1 H), 1.24–1.40 (m, 2 H), 1.54–1.81 (m, 2 H), 1.89–2.00 (m, 1 H), 4.27–4.39 (m, 1 H), 6.26 (d, 1 H, *J* = 4.2 Hz), 7.20–7.53 (m, 10 H). ¹³C NMR (125 MHz, CDCl₃): δ 19.18 (CH₂), 22.87 (CH₂), 31.54 (CH₂), 58.40 (CH), 63.09 (CH), 94.28 (C), 105.20 (CH), 111.84 (C), 126.31 (CH), 126.72 (CH), 127.83 (CH), 127.84 (CH), 128.01 (CH), 128.62 (CH), 141.74 (C), 145.12 (C), 155.84 (C). HRMS (EI): calcd for C₂₁H₂₀O₃ 320.1413, found 320.1402.

(3aR*,7S*,7aR*)-9,9-Diphenyl-4,5,6,7-tetrahydro-7a,3a-(epoxymethano)benzofuran-7-ol (trans-3a). ¹H NMR (500 MHz, CDCl₃): δ 0.60–0.83 (m, 1 H), 1.13–1.36 (m, 1 H), 1.37–1.56 (m, 1 H), 1.64–1.84 (m, 2 H), 2.14–2.29 (m, 1 H), 2.29–2.48 (m, 1 H), 4.14–4.30

(m, 1 H), 5.16 (d, 1 H, *J* = 2.9 Hz), 6.33 (d, 1 H, *J* = 2.9 Hz), 7.10–7.40 (m, 8 H), 7.56–7.65 (m, 2 H). ¹³C NMR (125 MHz, CDCl₃): δ 19.30 (CH₂), 28.97 (CH₂), 30.04 (CH₂), 61.12 (C), 72.26 (CH), 94.43 (C), 111.27 (C), 111.90 (CH), 125.23 (CH), 126.72 (CH), 126.86 (CH), 127.39 (CH), 128.14 (CH), 128.61 (CH), 143.05 (C), 145.00 (CH), 145.23 (C). HRMS (EI): calcd for C₂₁H₂₀O₃ 320.1413, found 320.1420. Anal. Calcd for C₂₁H₂₀O₃: C, 78.73; H, 6.29. Found: C, 78.71; H, 6.33. IR (KBr): 3529, 3023, 2991, 2948, 2893, 1955, 1699 cm⁻¹.

(3aR*,7R*,7aR*)-9,9-Diphenyl-4,5,6,7-tetrahydro-7a,3a-(epoxymethano)benzofuran-7-ol (cis-3a). ¹H NMR (500 MHz, CDCl₃): δ 1.18–1.31 (m, 1 H), 1.31–1.44 (m, 1 H), 1.47–1.73 (m, 3 H), 2.29–2.43 (m, 1 H), 2.60–2.65 (m, 1 H), 3.86–3.95 (m, 1 H), 4.89 (d, 1 H, *J* = 2.9 Hz), 6.27 (d, 1 H, *J* = 2.9 Hz), 7.10–7.17 (m, 1 H), 7.17–7.23 (m, 1 H), 7.23–7.30 (m, 2 H), 7.30–7.37 (m, 2 H), 7.37–7.43 (m, 2 H), 7.45–7.52 (m, 2 H). ¹³C NMR (125 MHz, CDCl₃): δ 16.13 (CH₂), 27.07 (CH₂), 27.29 (CH₂), 59.21 (C), 67.61 (CH), 97.40 (C), 109.24 (CH), 112.08 (C), 124.09 (CH), 125.01 (CH), 126.59 (CH), 127.20 (CH), 127.96 (CH), 128.57 (CH), 143.41 (C), 145.07 (C), 146.29 (CH). Mp: 132 °C. HRMS (EI): calcd for C₂₁H₂₀O₃ 320.1413, found 320.1420. Anal. Calcd for C₂₁H₂₀O₃: C, 78.73; H, 6.29. Found: C, 78.67; H, 6.29. IR (KBr): 3528, 3061, 2940, 2643, 1968, 1820, 1764, 1613 cm⁻¹.

(2aR*,6S*,7aR*)-2,2-Diphenyl-2a,3,4,5,6,7a-hexahydro-2H-oxeto[2,3-b]benzofuran-6-ol (trans-2b). ¹H NMR (C₆D₆, 500 MHz): δ 7.56–7.17 (m, 10 H), 6.26 (d, 1 H, *J* = 4.4 Hz), 4.34 (d, 1 H, *J* = 4.4 Hz), 3.99–3.93 (m, 1 H), 3.47 (s, 3 H), 1.85–1.68 (m, 2 H), 1.58–1.45 (m, 1 H), 1.45–1.32 (m, 1 H), 1.24–1.13 (m, 1 H), 0.95–0.83 (m, 1 H). ¹³C NMR (CDCl₃, 125 MHz): 154.34 (C), 144.79 (C), 141.70 (C), 128.23 (CH), 127.57 (CH), 127.42 (CH), 127.25 (CH), 126.14 (CH), 125.87 (CH), 112.96 (C), 104.47 (CH), 94.05 (C), 71.52 (CH), 58.20 (CH), 57.45 (C), 28.03 (CH₂), 22.66 (CH₂), 18.65 (CH₂). Mp: 97 °C. IR (KBr): 2944, 1958, 1694, 1598 1490 cm⁻¹.

(3aR*,7S*,7aR*)-9,9-Diphenyl-4,5,6,7-tetrahydro-7a,3a-(epoxymethano)benzofuran-7-ol (trans-3b). ¹H NMR (C₆D₆, 500 MHz): δ 7.66–7.59 (m, 2 H), 7.38–7.11 (m, 8 H), 6.38 (d, 1 H, *J* = 2.8 Hz), 5.13 (d, 1 H, *J* = 2.8 Hz), 3.92–3.87 (m, 1 H), 3.65 (s, 3 H), 2.31–2.16 (m, 1 H), 1.81–1.66 (m, 1 H), 1.51–1.34 (m, 2 H), 1.21–1.06 (m, 1 H), 0.77–0.57 (m, 1 H). ¹³C NMR (CDCl₃, 125 MHz): 145.07 (CH), 145.03 (C), 142.89 (C), 128.14 (CH), 127.75 (CH), 126.88 (CH), 126.37 (CH), 125.36 (CH), 124.64 (CH), 111.31 (CH), 110.82 (C), 93.39 (C), 81.08 (CH), 62.28 (C), 58.51 (CH), 28.72 (CH₂), 26.69 (CH₂), 19.86 (CH₂). Mp: 140 °C. IR (KBr): 2942, 1770, 1614, 1449 cm⁻¹.

(2aR*,7aR*)-2,2-Diphenyl-2a,3,4,5,6,7a-hexahydro-2H-oxeto[2,3-b]benzofuran (2c). ¹H NMR (500 MHz, CDCl₃): δ 0.90–1.04 (m, 1 H), 1.03–1.74 (m, 3 H), 2.10–2.38 (m, 4 H), 4.28 (m, 1 H), 6.19 (d, 1 H, *J* = 4.2 Hz), 7.01–7.74 (m, 10 H). ¹³C NMR (125 MHz, CDCl₃): δ 23.25 (CH₂), 23.30 (CH₂), 23.62 (CH₂), 24.02 (CH₂), 59.36 (CH), 94.69 (C), 105.45 (CH), 108.33 (C), 127.08 (CH), 127.52 (CH), 128.07 (CH), 128.30 (CH), 129.01 (CH), 129.83 (CH), 143.41 (C), 145.79 (C), 146.48 (C). Mp: 102 °C. HRMS (EI): calcd for C₂₁H₂₀O₂ 304.1463, found 304.1466. IR (KBr): 3063, 2967, 2887, 1966, 1898, 1656 cm⁻¹.

(3aR*,7aR*)-9,9-Diphenyl-4,5,6,7-tetrahydro-7a,3a-(epoxymethano)benzofuran (3c). ¹H NMR (CDCl₃, 500 MHz): δ 0.47–0.66 (m, 1 H), 1.05–1.21 (m, 1 H), 1.22–1.34 (m, 1 H), 1.37–1.61 (m, 2 H), 1.98–2.11 (m, 1 H), 2.17–2.33 (m, 2 H), 5.10 (d, 1 H, *J* = 2.9 Hz), 6.32 (d, 1 H, *J* = 2.9 Hz), 7.08–7.43 (m, 8 H), 7.54–7.67 (m, 2 H). ¹³C NMR (CDCl₃, 125 MHz): 20.81 (CH₂), 23.86 (CH₂), 29.78 (CH₂), 33.09 (CH₂), 58.64 (C), 94.07 (C), 111.45 (CH), 112.07 (C), 125.46 (CH), 126.14 (CH), 126.89 (CH), 127.34 (CH), 128.32 (CH), 128.68 (CH), 143.74 (C), 145.74 (CH), 146.06 (C); IR (KBr): 3278, 3058, 2975, 1956, 1887, 1662 cm⁻¹. Mp: 118 °C. HRMS (EI):

calcd for $C_{21}H_{20}O_2$ 304.1463, found 304.1454. IR (KBr): 3060, 2979, 2863, 1958, 1660 cm^{-1} .

(2aR*,6S*,7aR*)-6-Methyl-2,2-diphenyl-2a,3,4,5,6,7a-hexahydro-2H-oxeto[2,3-b]benzofuran-6-ol (trans-2d). 1H NMR (500 MHz, C_6D_6): δ 0.80–0.97 (m, 1 H), 0.97–1.09 (m, 1 H), 1.24–1.40 (m, 2 H), 1.40–1.55 (m, 5 H), 1.67–1.71 (m, 1 H), 3.91 (d, 1 H, J = 4.2 Hz), 6.03 (d, 1 H, J = 4.2 Hz), 6.90–7.20 (m, 6 H), 7.35–7.41 (m, 2 H), 7.44–7.75 (m, 2 H). ^{13}C NMR (125 MHz, C_6D_6): δ 20.55 (CH_2), 23.58 (CH_2), 26.87 (CH_3), 39.02 (CH_2), 58.92 (CH), 67.35 (C), 94.42 (C), 105.05 (CH), 109.94 (C), 126.59 (CH), 126.88 (CH), 127.61 (CH), 127.74 (CH), 127.93 (CH), 128.65 (CH), 142.85 (C), 145.82 (C), 158.46 (C). HRMS (EI): calcd for $C_{22}H_{22}O_3$ 334.1569, found 334.1567.

(2aR*,6R*,7aR*)-6-Methyl-2,2-diphenyl-2a,3,4,5,6,7a-hexahydro-2H-oxeto[2,3-b]benzofuran-6-ol (cis-2d). 1H NMR (500 MHz, C_6D_6): δ 1.00–1.08 (m, 1 H), 1.10–1.19 (m, 1 H), 1.24–1.41 (m, 4 H), 1.41–1.50 (m, 1 H), 1.63–1.71 (m, 1 H), 1.82–1.93 (m, 1 H), 3.92 (d, 1 H, J = 4.2 Hz), 6.05 (d, 1 H, J = 4.2 Hz), 6.90–7.21 (m, 6 H), 7.34–7.40 (m, 2 H), 7.53–7.58 (m, 2 H). ^{13}C NMR (125 MHz, C_6D_6): δ 20.28 (CH_2), 23.33 (CH_2), 26.06 (CH_3), 38.93 (CH_2), 58.54 (CH), 67.04 (C), 94.33 (C), 105.12 (CH), 109.62 (C), 126.70 (CH), 127.25 (CH), 127.73 (CH), 127.86 (CH), 128.09 (CH), 128.65 (CH), 142.47 (C), 145.83 (C), 158.72 (C). HRMS (EI): calcd for $C_{22}H_{22}O_3$ 334.1569, found 334.1567.

(3aS*,7S*,7aS*)-7-Methyl-9,9-diphenyl-4,5,6,7-tetrahydro-7a,3a-(epoxymethano)benzofuran-7-ol (trans-3d). 1H NMR (500 MHz, C_6D_6): δ 0.79–0.89 (m, 1 H), 1.49 (s, 3 H), 1.58–1.65 (m, 2 H), 1.66–1.75 (m, 1 H), 1.75–1.84 (m, 1 H), 1.95–1.99 (m, 1 H), 1.99–2.07 (m, 1 H), 4.62 (d, 1 H, J = 2.9 Hz), 5.82 (d, 1 H, J = 2.9 Hz), 6.91–6.98 (m, 2 H), 7.05–7.12 (m, 4 H), 7.40–7.44 (m, 2 H), 7.45–7.50 (m, 2 H). ^{13}C NMR (125 MHz, C_6D_6): δ 16.44 (CH_2), 23.06 (CH_3), 25.94 (CH_2), 32.62 (CH_2), 58.99 (C), 70.78 (C), 95.70 (C), 110.35 (CH), 114.26 (C), 125.40 (CH), 125.89 (CH), 126.68 (CH), 127.14 (CH), 128.52 (CH), 128.79 (CH), 144.35 (C), 146.25 (C), 146.85 (CH). R_f : 0.625. HRMS (EI): calcd for $C_{22}H_{22}O_3$ 334.1569, found 334.1551.

(3aS*,7R*,7aS*)-7-Methyl-9,9-diphenyl-4,5,6,7-tetrahydro-7a,3a-(epoxymethano)benzofuran-7-ol (cis-3d). 1H NMR (500 MHz, C_6D_6): δ 1.24–1.48 (m, 6 H), 1.48–1.59 (m, 1 H), 1.68–1.79 (m, 1 H), 2.43–2.49 (m, 1 H), 2.59–2.69 (m, 1 H), 4.42 (dd, 1 H, J^1 = 1.1 Hz, J^2 = 2.8 Hz), 5.89 (dd, 1 H, J^1 = 1.1 Hz, J^2 = 2.8 Hz), 6.88–7.21 (m, 6 H), 7.30–7.35 (m, 2 H), 7.44–7.50 (m, 2 H). ^{13}C NMR (125 MHz, C_6D_6): δ 17.24 (CH_2), 23.62 (CH_3), 25.31 (CH_2), 31.33 (CH_2), 60.15 (C), 69.21 (C), 98.73 (C), 108.17 (CH), 114.58 (C), 125.03 (CH), 125.42 (CH), 126.75 (CH), 127.14 (CH), 128.52 (CH), 128.90 (CH), 144.68 (C), 146.01 (C), 147.31 (CH). HRMS (EI): calcd for $C_{22}H_{22}O_3$ 334.1569, found 334.1551.

■ COMPUTATIONAL METHODS

All of the structures calculated for the hydrogen-bonded interaction between H_2CO and CH_3OH in Figure 4 were optimized using (U)MP2/6-31+G(d,p).²¹ The PB reactions of **1a,c** with **BP** were calculated at the (U)B3LYP/6-31+G(d)²² level of theory. All these calculations were performed using the Gaussian 03 suite programs.²³ The energies and optimized Cartesian coordinates are summarized in the Supporting Information.

■ RESULTS AND DISCUSSION

Effects of Temperature and Concentration on Product Selectivity in a Photocycloaddition Reaction of **1a with Benzophenone (BP).** First, the temperature and concentration effect on regio- and stereoselectivity in the PB reaction of **1a** with

BP was investigated using a high-pressure Hg lamp (150 W) through a Pyrex filter ($h\nu > 300$ nm) in a dried and degassed toluene solution (eq 1 and Table 1). In accordance with hydroxy-group directivity, a cis-configured oxetane **3a** is the preferred result of the PB reaction. As shown in entries 1–5 (**[1a]** = 340 mM), at a higher temperature (60 °C) the trans-selective formation was observed in the lower-substituted oxetane **2a** (entry 1). However, a slight, but nonetheless apparent, cis-selective formation was detected in the higher-substituted oxetane **3a**. Compounds **5–8** were observed as minor products in the photochemical reactions. The trans-selectivity of **2a** increased very slightly with a decrease in the reaction temperature, e.g., 70/30 at 60 °C (entry 1) and 82/18 at –75 °C (entry 5). By contrast, the stereoselectivity of **3a**, in which the oxetane ring is closely located to the hydroxyl group, was drastically changed from cis-selectivity at high-temperatures to trans-selectivity at low temperatures at **[1a]** = 340 mM, i.e., from a ratio of 42/58 at 60 °C (entry 1) to a ratio of 72/28 at –75 °C (entry 5). The regioselectivity **2a/3a** was also found to be largely temperature-dependent. Thus, the formation of **3a** increased with an increase in the reaction temperature, e.g., from a ratio of *trans-2a/3a* = 48/52 and *cis-2a/3a* = 35/65 at –75 °C (entry 5) to a ratio of *trans-2a/3a* = 20/80 and *cis-2a/3a* = 8/92 at 60 °C (entry 1). The regioselectivity of the higher-substituted oxetane **3a** was significantly higher in the cis-isomer than that in the trans-isomer. The effect of temperature on regioselectivity in the *trans-2a/3a* was very similar to our previous observation in the PB reaction with 2-methylfuran, i.e., a lower-substituted/higher-substituted oxetane = 42/58 at –77 °C and 19/81 at 61 °C.²⁴

To obtain further insight into the hydroxy-group effect on stereoselectivity and regioselectivity, the effect of concentration on selectivity in the formation of compounds **2a** and **3a** was examined (entries 6–11, Figures 1 and 2). First, the effects of concentration on the regioselectivity of *trans*- and *cis-2a/3a* were examined at 60 °C (entries 6–8) and –75 °C (entries 9–11). At 60 °C (Figure 1a,b), concentration had no effect on regioselectivity for either *trans*- or *cis*-isomers in a concentration range of 10 mM < **[1a]** < 1000 mM; for *trans*-isomers, *trans-2a/3a* \sim 22/78 (Figure 1a); for *cis*-isomers, *cis-2a/3a* \sim 8/92 (Figure 1b). These results are consistent with the general phenomena that entropically disfavored aggregations are no longer possible at such high temperatures. However, at low temperatures, such as –75 °C (entries 9–11), a significant effect of concentration was observed on regioselectivity in *cis*-isomers *cis-2a/3a* (Figure 1d). The ratio was changed from 47/53 at **[1a]** = 1000 mM to 19/81 at **[1a]** = 10 mM. An almost negligible effect was observed in the *trans*-isomer *trans-2a/3a* (Figure 1c), i.e., from 53/47 at **[1a]** = 1000 mM to 45/55 at **[1a]** = 10 mM. Thus, the higher-substituted *cis*-configured oxetane *cis-3a* was preferably formed at a low concentration of **1a**.

A similar effect of concentration was also observed in the stereoselectivity of *trans/cis-2a* and *-3a* (Figure 2). At high temperature, 60 °C, concentration had no effect on the stereoselectivity of **2a** and **3a** (entries 6–8, Figure 2a,b). However, a notable effect of concentration at –75 °C was observed in the formation of **3a** (entries 9–11, Figure 2d). Thus, the formation of *cis-3a* increased remarkably (from 19% to 49%) with a decrease in the concentration of **1a**. A very small increase (from 15% to 21%) in the formation of *cis-2a* was observed (Figure 2c). The effects of concentration shown in Figures 1 and 2 clearly indicate that the intermolecular hydrogen-bonding interaction, e.g., the aggregation of **1a** (Scheme 1), plays a crucial

Table 1. Effects of Temperature and Concentration on the Product Ratios in the PB Reaction of **1a** with BP^a

(1)

entry	temp/°C	[1a]/mM	products and yields ^b /%				stereoselectivity ^c		regioselectivity ^d	
			<i>trans</i> - 2a	<i>cis</i> - 2a	<i>trans</i> - 3a	<i>cis</i> - 3a	<i>trans</i> / <i>cis</i> - 2a	<i>trans</i> / <i>cis</i> - 3a	<i>trans</i> - 2a / 3a	<i>cis</i> - 2a / 3a
1	60	340	7	3	28	37	70/30	42/58	20/80	8/92
2	20	340	12	4	30	36	73/27	45/55	28/72	11/89
3	0	340	15	4	32	34	79/21	48/52	33/67	11/89
4	−45	340	28	7	39	23	80/20	63/37	42/58	23/77
5	−75	340	31	7	33	13	82/18	72/28	48/52	35/65
6	60	1000	7	3	25	36	70/30	41/59	22/78	8/92
7	60	100	6	3	22	32	67/33	41/59	21/79	7/93
8	60	10	8	4	30	42	67/33	42/58	21/79	8/92
9	−75	1000	39	7	34	8	85/15	81/19	53/47	47/53
10	−75	100	30	7	34	20	81/19	63/37	47/53	26/74
11	−75	10	22	6	27	26	79/21	51/49	45/55	19/81
12 ^e	20	340	20	0	44	0	>97/3	>97/3	31/69	—

^a The photoreaction of **1a** with benzophenone (BP) was performed in degassed toluene with a high-pressure Hg-lamp through a Pyrex filter. The recovered BP was less than 3% after 6 h of irradiation. Small amounts of compounds **5–8** (~10%) were detected as minor products in the photolysate. The mass balances were >83%. ^b The product yields were determined on the basis of ¹H NMR (500 MHz) peak areas (error ±3%). Triphenylmethane (Ph₃CH) was used as an internal standard. The ratios in parentheses are the normalized *trans*/*cis* stereoselectivity of compounds **2a** and **3a**. ^c The stereoselectivities were normalized to 100%. ^d The regioselectivities were normalized to 100%. ^e The reaction was performed in a dry and degassed DMSO solution.

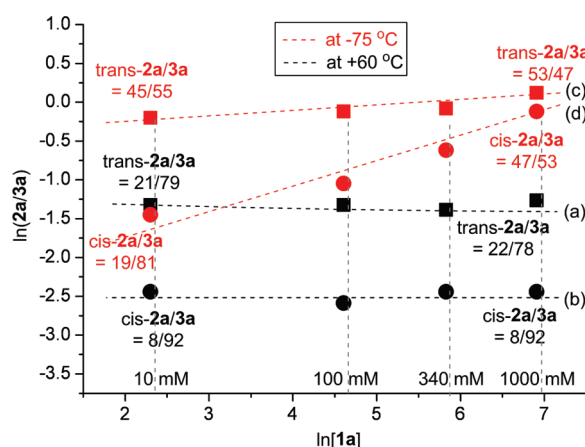


Figure 1. Concentration effect of **1a** on regioselectivity in the formation of oxetanes **2a** and **3a**, which were normalized to 100%: (a) *trans*-**2a**/**3a** at 60 °C, (b) *cis*-**2a**/**3a** at 60 °C, (c) *trans*-**2a**/**3a** at −75 °C, and (d) *cis*-**2a**/**3a** at −75 °C.

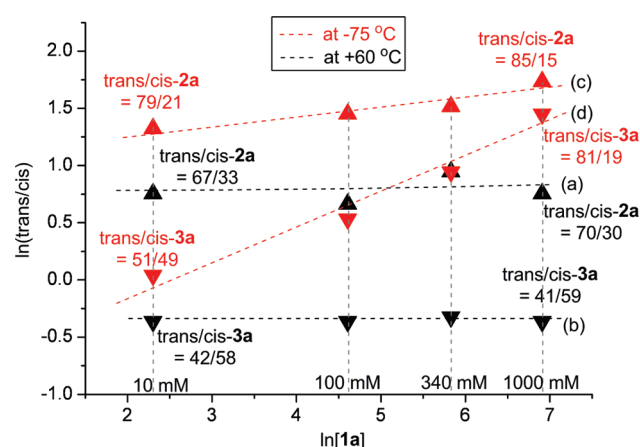


Figure 2. The effects of the concentration of **1a** on stereoselectivity in the formation of oxetane **2a** and **3a**, which were normalized to 100%: (a) *trans*/*cis*-**2a** at 60 °C, (b) *trans*/*cis*-**3a** at 60 °C, (c) *trans*/*cis*-**2a** at −75 °C, and (d) *trans*/*cis*-**3a** at −75 °C.

role in controlling both regio- and stereoselectivity in the formation of oxetanes. In fact, the ¹H NMR resonance of the

hydroxyl proton of **1a** was temperature and concentration sensitive (Figures 3a ,b). Thus, a downfield shift of the OH

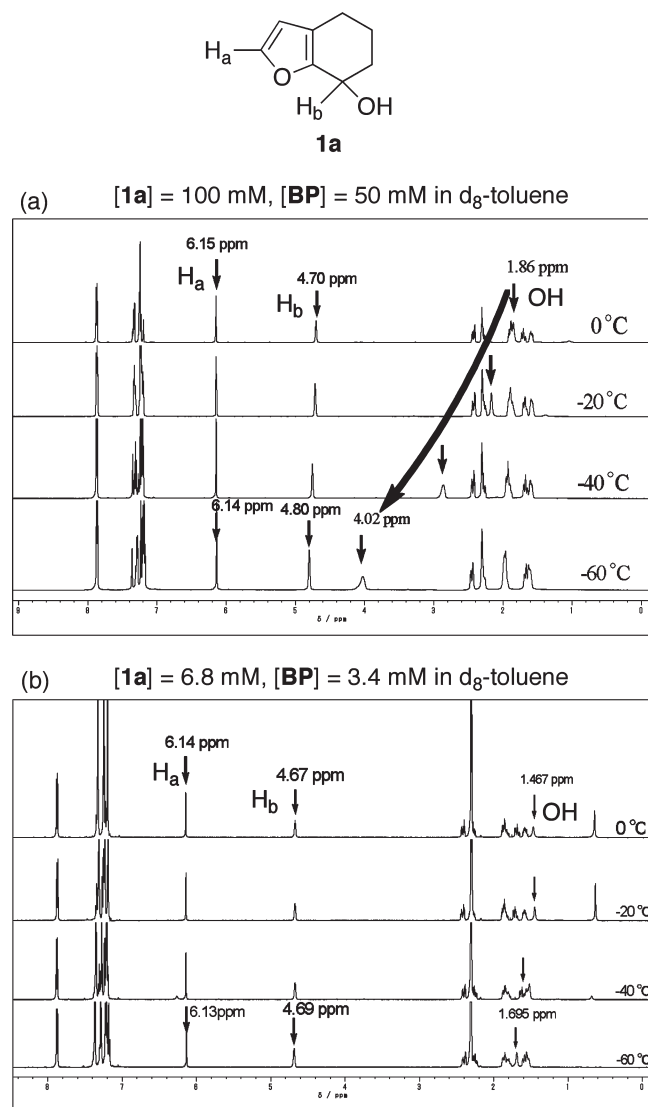
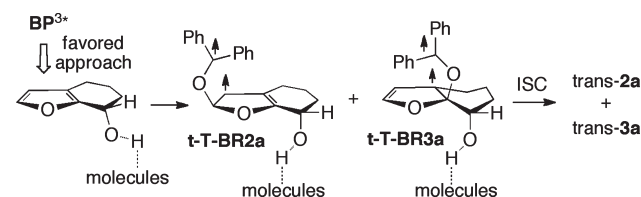


Figure 3. Variable temperature ^1H NMR spectrum of **1a** (500 MHz, C_7D_8) at (a) higher concentration of **[1a]**, i.e., **[1a]** = 100 mM and **[BP]** = 50 mM, and (b) lower concentration of **[1a]**, i.e., **[1a]** = 6.8 mM and **[BP]** = 3.4 mM.

proton resonance was observed from δ 1.86 (0 °C) to 4.02 (−60 °C) with a decrease in temperature when compound **1a** (100 mM) was dissolved in dried toluene- d_8 (Figure 3a). A similar change in the hydroxyl proton resonance was also observed in the absence of benzophenone. No change was observed in the resonance of the ortho-protons of benzophenone (δ 7.88 ppm). Of note, a small, but significant, shift was detected in the resonance of the proton H_b , i.e., δ 4.70 (0 °C) and 4.80 (−60 °C). No movement was observed in the resonance of the H_a proton, δ 6.15 (0 °C) and 6.14 (−60 °C). This observation supports that the aggregation is the intermolecular hydrogen bonding around the hydroxyl group. A small shift of the resonance of the OH proton, i.e., δ 1.47 (0 °C) and 1.70 (−60 °C), was observed at the lower concentrations of **1a** (6.8 mM) and **BP** (3.4 mM) in dried toluene- d_8 (Figure 3b). Thus, the entropically disfavored intermolecular interaction will be diminished under the conditions of low concentration and high temperature. Under these conditions (10 mM and 60 °C), the cis-configured **3a** was found to be a major product, *trans-2a/cis-2a/trans-3a/cis-3a* = 10/4/35/51 at a

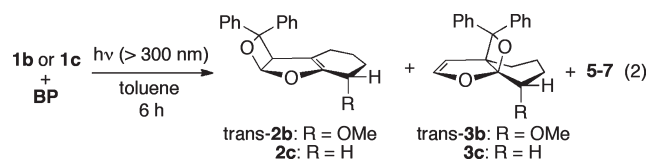
Scheme 4



mass balance of 84% (entry 8 in Table 1). The ratio was normalized to 100%. Of note, *trans*-selectivity was found for **2a**, but *cis*-selectivity was found for **3a**, although the steric bulk of a hydroxyl group is much larger than that of a hydrogen atom.²⁵ These results strongly suggest that a hydrogen-bonding interaction in the PB reaction of **1a** plays an important role in controlling regio- and stereoselectivity at a low concentration of **1a** in a nonpolar solvent, although negligible hydrogen-bonding stabilization is expected in the interaction of the n,π^* excited carbonyl with alcohol (vide infra).¹² Under conditions of low temperature and high concentration, the *trans*-configured oxetanes were selectively formed, i.e., *trans-2a/cis-2a/trans-3a/cis-3a* = 44/8/37/11 (entry 9 in Table 1). These results clearly indicate that the aggregation plays a crucial role in controlling the face selectivity. Therefore, only the *trans*-isomers of **2a** and **3a** were detected in DMSO, which is a good hydrogen-bond acceptor (entry 12 in Table 1). Aggregation would suppress the approach of BP^{3*} from the side of the hydroxyl group in **1a** to afford the *trans*-selective formation of the intermediary triplet 1,4-diyls *t-T-BR2a* and *t-T-BR3a* (Scheme 4).

Photocycloaddition Reaction of 1b,c with Benzophenone (BP). To obtain more information about the hydroxyl group effect on regio- and stereoselectivity, the PB reactions of the hydroxyl-protected methyl ether **1b**²⁶ and tetrahydrobenzofuran (**1c**) with **BP** were investigated (eq 2, Table 2). As shown in entries 1–6, the clean formation of the tricyclic oxetanes **2b,c** and **3b,c** were observed with high mass balances, and thus, the determination of the product ratios was feasible. The temperature-dependent change of the regioselectivity observed in the PB reactions of both **1b** and **1c** was quite similar to that detected in *trans-2a/3a*; compare entries 1–5 with entries 1–5 in Table 1. In sharp contrast to the stereoselectivity observed in the reaction with **1a**, i.e., *trans*-selectivity in **2a** and *cis*-selectivity in **3a**, only *trans*-configured oxetanes **2b** and **3b** were detected. We could not observe the *cis*-isomers using ^1H NMR (500 MHz) spectroscopic analyses. No effect of concentration was observed for product selectivity (entries 5 and 6). These results clearly indicate that the notable concentration-dependent change of regioselectivity in *cis-2a/3a* (Figure 1) and the stereoselectivity in *trans/cis-3a* (Figure 2) were due to the aggregation around the hydroxyl group in **1a**.

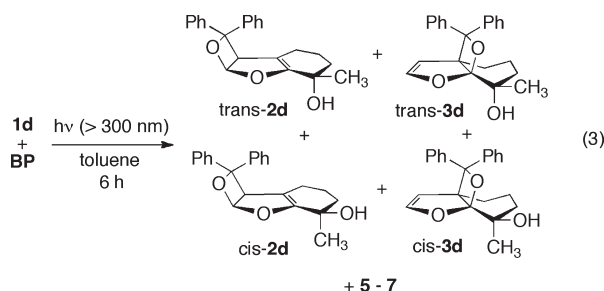
The PB Reaction of 1d with Benzophenone (BP). To gain insight into the steric effect on diastereoselectivity in oxetane formation, the methyl-substituted alcohol **1d** was used for a PB reaction with benzophenone (BP^{3*}), as shown by eq 3 and in Table 3. *Cis*-stereoselectivity was apparent in the formation of **3d**, i.e., *trans/cis-3d* = 24/76 at 60 °C (entry 1), which was higher than that obtained in **3a**, *trans/cis-3a* = 42/58 (entry 1 in Table 1). As observed for stereoselectivity in **2a** and **3a**, a significant decrease in the *cis*-selectivities of **2d** and **3d** was obtained with a decrease in the reaction temperature (entries 1–5). At a low concentration of **1d**, the *cis*-selectivity in **3d** was higher than that at higher concentration of **1d**, as shown by

Table 2. Effects of Temperature and Concentration on the Product Ratios in the PB Reaction of **1b,c** with BP^a

entry	temp/°C	concn /mM	products and yields ^b /%				regioselectivity ^c (mass balance/%) ^d	
			for 1b + BP		for 1c + BP			
			trans-2b	trans-3b	2c	3c	trans-2b/3b	2c/3c
1	60	340	20	52	13	66	28/72 (82)	16/84 (87)
2	20	340	15	32	16	61	31/69 (80)	21/79 (83)
3	0	340	16	33	16	61	32/68 (84)	21/79 (83)
4	−45	340	30	50	26	59	37/63 (81)	31/69 (92)
5	−75	340	34	51	28	52	40/60 (87)	35/65 (87)
6	−75	6.8	27	41	23	46	40/60 (96)	34/66 (91)

^a The photoreaction of **1b** or **1c** with benzophenone (BP) was performed in degassed toluene with a high-pressure Hg-lamp through a Pyrex filter. The recovered BP was less than 3% after 6 h of irradiation. Small amounts of compounds **5–7** (<10%) were detected as a minor product in the photolysate.

^b The product yields were determined on the basis of ¹H NMR (500 MHz) peak areas (error ±3%). Triphenylmethane (Ph₃CH) was used as an internal standard. ^c The regioselectivities were normalized to 100%. ^d The values represent the total yields of **2**, **3**, **5**, and the recovered BP.

Table 3. Product Ratios in the PB Reaction of **1d** with BP^a

entry	temp/°C	[1d]/mM	products and yields ^b /%				stereoselectivity ^c		regioselectivity ^d	
			trans-2d	cis-2d	trans-3d	cis-3d	trans/cis-2d	trans/cis-3d	trans-2d/3d	cis-2d/3d
1	60	340	3	4	12	39	44/56	24/76	19/81	9/91
2	20	340	4	5	18	55	42/58	25/75	17/83	8/92
3	0	340	7	6	23	58	53/47	29/71	22/78	9/91
4	−46	340	16	10	30	38	62/38	44/56	34/66	20/80
5	−75	340	21	9	29	22	70/30	57/43	42/58	30/70
6	60	6.8	2	3	7	18	40/60	26/74	23/77	14/86
7	0	6.8	4	4	11	30	48/52	26/74	25/75	12/88
8	−75	6.8	8	8	17	34	51/49	32/68	33/67	19/81

^a The photoreaction of **1d** with benzophenone (BP) was performed in degassed toluene with a high-pressure Hg-lamp through a Pyrex filter. The recovered BP was less than 3% after 6 h irradiation. Small amounts of compounds **5–7** (~10%) were detected as minor products in the photolysate. The mass balances were >83%. ^b The product yields were determined on the basis of ¹H NMR (500 MHz) peak areas (error ±3%). Triphenylmethane (Ph₃CH) was used as an internal standard. The ratios in parentheses are the normalized trans/cis-stereoselectivity of compounds **2d** and **3d**. ^c The stereoselectivities were normalized to 100%. ^d The regioselectivity were normalized to 100%.

entries **5** and **8**. The notable temperature and concentration effects can be reasonably explained by the existence of the hydrogen-bonded aggregation, which decreases the cis-selectivity in **3d**. Thus, a hydrogen-bonded aggregation at low temperature occurs in some cases even with a low concentration of the substrate. The cis-selectivity in **3d** was higher than that in **3a**; therefore, the steric effect was also responsible for increasing

cis-selectivity. The regioselectivity observed in the PB reaction of **1d**, i.e., **2d/3d**, was quite similar to that detected in the PB reaction of **1a**.

Hydrogen-Bonding Interaction of the Ground-State and the n,π^* Triplet Excited-State Formaldehyde with Methanol. As mentioned in the Introduction, Morokuma and Iwata reported a very small energetic stabilization of 0.2–0.4 kcal mol^{−1} for the

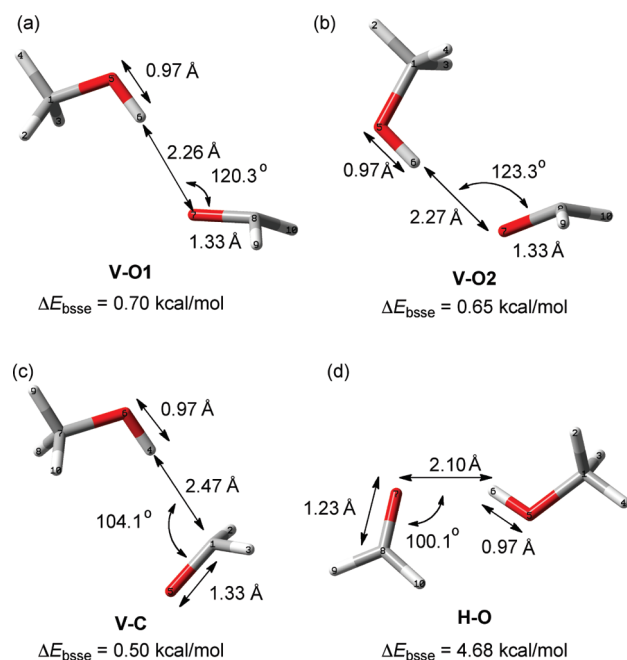


Figure 4. Hydrogen-bonded structures and stabilization energies (ΔE_{bsse}) at the (U)MP2/6-31+G(d,p) level of theory after BSSE corrections between a and c for the n,π^* excited state H_2CO and CH_3OH and (d) for the ground state H_2CO and CH_3OH .

interaction between the n,π^* triplet excited state formaldehyde (H_2CO) and H_2O , which was found to be about $3.5 \text{ kcal mol}^{-1}$ smaller than the stabilization energy for the hydrogen-bonding interaction of ground-state H_2CO with H_2O .¹² To clarify the structures of the hydrogen-bonded complexes and stabilization energies of a similar interaction with alcohols, we first calculated the equilibrium structures and the stabilization energies of ground-state and n,π^* triplet excited-state H_2CO with methanol (CH_3OH) at the (U)MP2/6-31+G(d,p) level of theory (Figure 4). As reported for the $\text{H}_2\text{CO}-\text{H}_2\text{O}$ interaction, the structures of the vertical approach of the hydroxyl group to the H_2CO plane, i.e., **V-O1**, **V-O2**, **V-C**, were optimized as equilibrium structures in the interaction of the triplet excited H_2CO and CH_3OH , in which the stabilization energies were calculated to be 0.70, 0.65, and 0.50 kcal mol^{-1} , after the counterpoise (BSSE) corrections, respectively. In the ground-state calculations, the structure of the horizontal approach of the hydroxyl group, **H-O**, was optimized at the same level of theory. The interaction energy was found to be $4.68 \text{ kcal mol}^{-1}$ after the BSSE correction. Such horizontal complexes were not found to be equilibrium structures for the triplet-state calculations. This result is quite reasonable, since the direction of the original n -orbital was changed to electrophilic after the n,π^* electronic excitation (Scheme 3b). The ab initio calculations clearly indicate that an almost negligible stabilization effect is expected between the hydroxyl group and the n,π^* triplet-state carbonyl (Figure 4). The stabilization energies for **V-O1** and **H-O** were also estimated by more conventional low-cost (U)DFT methods at the UB3LYP, UM05, and UM06 with the 6-31+G(d) basis set, although the DFT methods are known to overestimate dispersion forces.²⁷ Low-cost calculations are needed for the PB reactions of **1** with **BP**. The stabilization energies were established at 2.1, 2.6, and 3.2 kcal/mol for **V-O1**, respectively, which were higher values than those obtained using the UMP2 method. However, the stabilization energies calculated for the

triplet state were significantly smaller than those calculated for the ground state complex **H-O**: 4.5, 6.0, and 6.0 kcal/mol , respectively. Even with the low-cost calculations, the hydrogen-bonded stabilization energy in the triplet state was estimated to be significantly smaller than that in the ground state. However, our experimental studies clearly indicate that the hydroxy group indeed directs the regio- and stereochemical outcomes in the PB reaction of **1a** with **BP**, i.e., the selective formation of *cis*-**3a,d** at a low concentration of **1a,d**.

Computational Studies on the PB Reaction of 1c. To elucidate the role of the hydroxy group, the Mulliken-charge change on the oxygen atom of H_2CO was calculated in a model PB reaction of the triplet excited formaldehyde H_2CO^{3*} with **1c** at the UB3LYP/6-31+G(d) level of theory, leading to the formation of the intermediary triplet biradical **T-BR3-in** (Figure 5).^{22,28} As Figure 5b (red line) clearly shows, the negative charge density on the oxygen atom of H_2CO^{3*} increased from a value of -0.14 to -0.25 with a decrease in the distance, r , of $\text{C}(8)-\text{O}$, i.e., from ca. 350 to 230 pm within the sum of the van der Waals radii of carbon (170 pm) and oxygen (152 pm). The scan-mode calculations clearly showed that the charge transfer occurred from the alkene part (furan) to the electrophilic oxygen of the n,π^* excited H_2CO during a decrease in the atom distance of $\text{C}(8)-\text{O}$. At the local energy minimum structure (Figure 5c), i.e., exciplex, at a distance, r , of 253 pm, the negative charge of the carbonyl oxygen was calculated to be -0.25 , which is the maximum value at the same level of theory. The Mulliken charge on the carbonyl oxygen of the ground-state H_2CO was found to be -0.30 at the same level of theory. Thus, the charge transfer²⁹ during the formation of the exciplex occurred to make the oxygen of H_2CO^{3*} nucleophilic, i.e., a good hydrogen-bonding acceptor. During the bond formation between **C(8)** and the carbonyl oxygen with a small energy barrier of ca. 0.9 kcal/mol , the charge on the oxygen atom was found to decrease to ca. -0.10 (Figure 5b), which was smaller than the value of H_2CO^{3*} (-0.15). The decrease in the negative charge is rationalized by the resonance structure of **T-BR3-in** in Figure 5, i.e., the character of $\text{O}^{\bullet+}-\text{C}^-$.³⁰ The electron delocalization from the 2p AO of the oxygen to the radical p-orbital is responsible for the resonance structure and the perpendicular orientation of the carbonyl moiety with a furan ring in the optimized structure of **T-BR3-in** (Figure 5). Thus, the basicity of the oxygen atom derived from H_2CO in **T-BR3-in** is weaker than that of the oxygen atom in H_2CO^{3*} .

As shown in Figure 5, the transition-state energy for the generation of **T-BR3-in** from the intermediary exciplex was calculated to be lower than the energy of the reactants (**1c** + H_2CO^{3*}). Thus, the process is not the selectivity-differentiating step, i.e., the rate-determining step, in the PB reaction of the small molecule H_2CO^{3*} . However, the transition state for generating the intermediary triplet biradicals becomes important for diastereoselectivity in the PB reaction of the more-steric bulk benzophenone triplet state BP^{3*} (Figure 6 and Scheme 5). As shown in Figure 6, the basicity of the benzophenone oxygen, i.e., the Mulliken charge on the oxygen atom, increases with a decrease in the bond distance $\text{C}(8)-\text{O}$, which is quite similar to the charge-change calculated for H_2CO^{3*} (Figure 5). Of note, the transition state **TS** was calculated to be higher in energy than that of the reactants **1c** and BP^{3*} (Scheme 5). The negligible basicity was also calculated for the biradical **T-BR3c-in**. Thus, the charge of the oxygen atom in **T-BR3c-in** was found to be -0.13 , although the charge of the triplet benzophenone (BP^{3*}) was found to

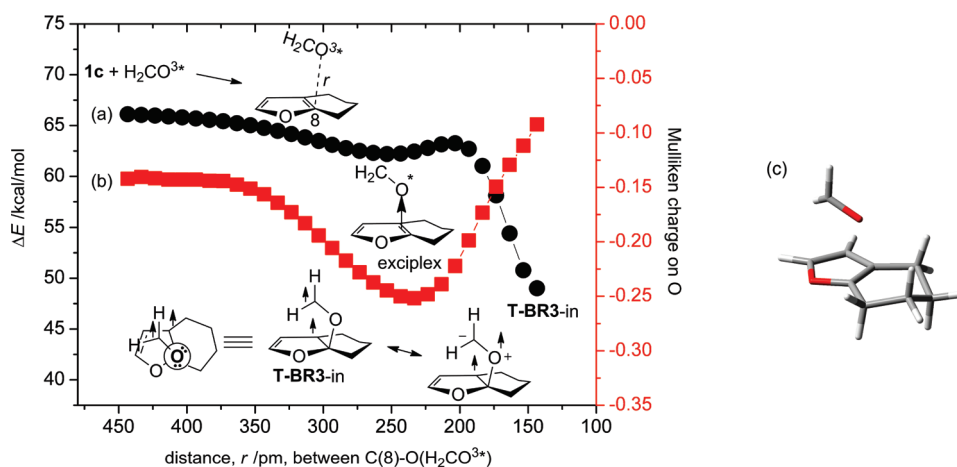


Figure 5. The UB3LYP/6-31+G(d) analysis of (a) the energy profile and (b) the distance-dependent change of the Mulliken charge of the oxygen atom of H_2CO during the bond-formation of the triplet n, π^* excited formaldehyde (H_2CO) with the furan derivative 1c. (c) The structure at the distance of $r = 253$ pm.

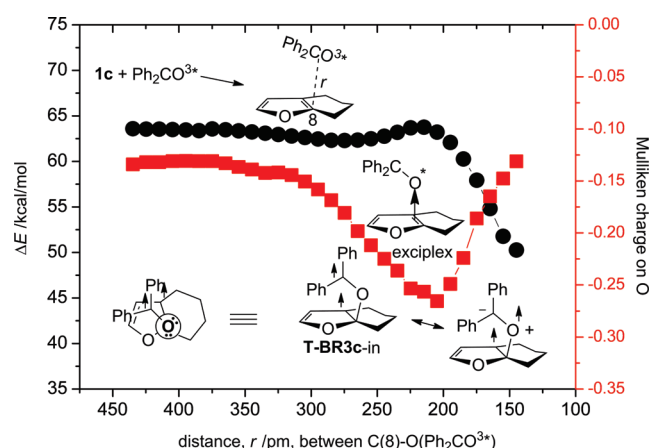
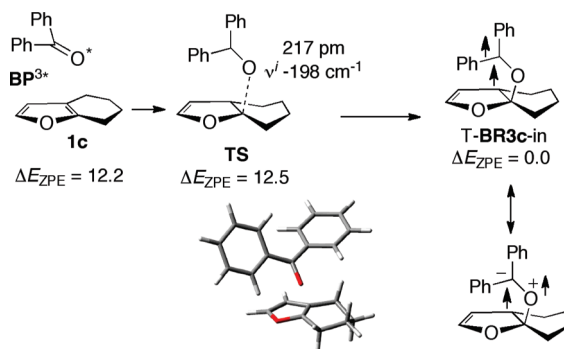


Figure 6. The UB3LYP/6-31+G(d) analysis of (a) the energy profile and (b) the distance-dependent change of the Mulliken charge of the oxygen atom of Ph_2CO (BP) during the bond formation of the triplet n, π^* excited benzophenone (Ph_2CO) with the furan derivative 1c.

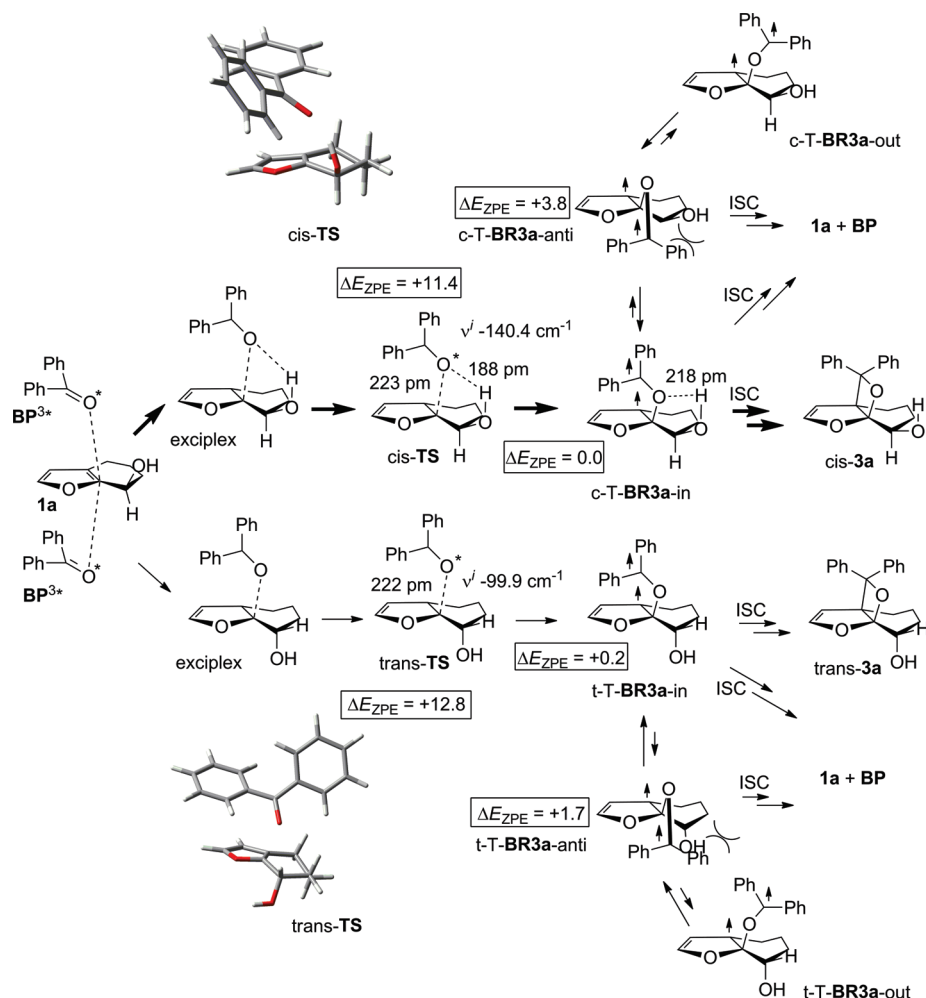
be -0.20 at the same level of theory. This clearly indicates that the oxygen atom derived from BP in the triplet biradicals is not the hydrogen-bond acceptor. The charge density in TS was calculated to be -0.25 , which was larger than those in either the biradical or BP^{3*} , and therefore, it should be nucleophilic.

Computational Studies on the PB Reaction of 1a with BP^{3*} . As mentioned above in the computational studies, hydrogen-bonding stabilization is possible only during the formation of the charge-transferred exciplex. To prove the stabilization effect, the energy profile of the PB reaction of 1a with the triplet state of benzophenone BP^{3*} was calculated at the UB3LYP/6-31+G(d) level of theory (Scheme 6). Indeed, the transition state *cis*-TS ($\Delta E = 11.4$ kcal/mol) with an imaginary frequency of $\nu^i - 140.4$ cm^{-1} , which produces *cis*-3a via the triplet biradical c-T-BR3a-in after the intersystem crossing (ISC) process, was calculated to be lower in energy by 1.4 kcal/mol than the transition state *trans*-TS ($\Delta E_{\text{ZPE}} = 12.8$ kcal/mol) with an imaginary frequency of $\nu^i - 99.9$ cm^{-1} , which affords *trans*-3a via t-T-BR3a-in. As expected from the negligible basicity of the oxygen atom in the triplet

Scheme 5. Optimized Structures and Energies (kcal/mol) of the Transition State TS and the inside Conformer of the Biradicals T-BR3c-in Derived from the Reaction of BP^{3*} with 1c at the UB3LYP/6-31+G(d) Level of Theory



biradicals, the *cis*-configured biradical c-T-BR3a-in was calculated to be only 0.2 kcal/mol more stable than the *trans*-configured biradical t-T-BR3a-in. The hydrogen-bond distance of 218 pm was longer than that found in the transition state *cis*-TS (188 pm). Thus, the energetic stabilization in the exciplex was found to be significantly larger than that in the intermediary triplet biradicals. The preferred formation of *cis*-3a in our experiment under a low concentration of 1a, where the aggregation would be suppressed, can be reasonably explained by the energetic preference of the formation of the *cis*-configured biradical c-T-BR3a-in. The inside conformer was calculated to be more stable than the anticonformer c-T-BR3a-anti by 3.8 kcal/mol, which would produce the starting compounds 1a and benzophenone after the ISC process and followed by the C-O bond breaking. Indeed, the optimization of the singlet state of the anti biradical c-S-BR3a-anti produced 1a and BP at the broken-symmetry (U)B3LYP/6-31+G(d) level of theory, which clearly indicated that the C-O bond cleavage is a process without barrier and is faster than the conformational change to the productive inside conformer. The anticonformer of the *trans*-configured biradical t-T-BR3a-anti was also calculated to be less stable by comparison with the inside conformer t-T-BR3a-in,

Scheme 6. Energy Profiles of the PB Reaction of 1a with BP^{3*} at the UB3LYP/6-31+G(d) Level of Theory^a

^a The energies (ΔE_{ZPE} in kcal mol^{-1}) were relative to the energy for c-T-BR3a-in after the zero-point energy corrections.

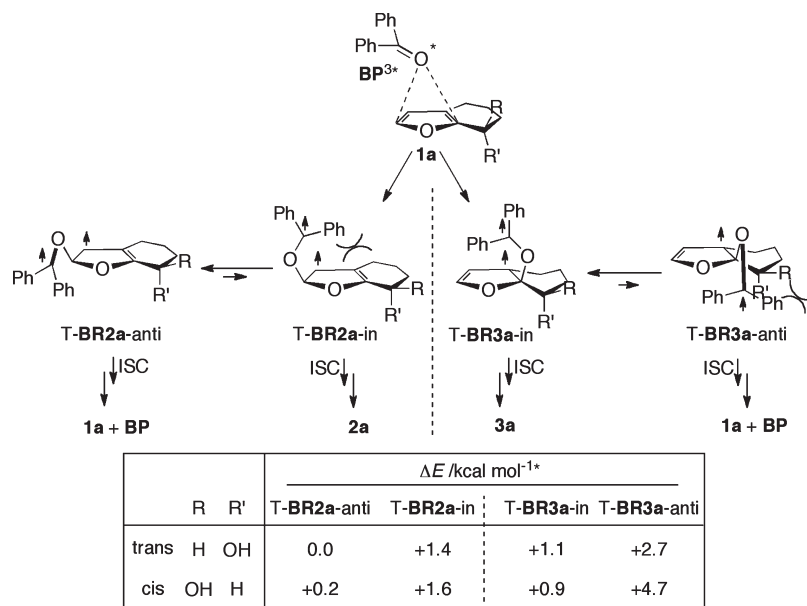
although the energy difference ($\Delta\Delta E_{\text{ZPE}} = 1.5 \text{ kcal mol}^{-1}$) was smaller than the cis-isomer c-T-BR3a ($\Delta\Delta E_{\text{ZPE}} = 3.8 \text{ kcal mol}^{-1}$). The energetic preference of the inside conformers can be reasonably explained by the steric repulsion between the phenyl ring with the cyclohexane ring system in the antic-former. Although the outside conformers t-T-BR3a-out and c-T-BR3a-out are also the possible structures of the intermediary triplet biradicals, the conformers were not calculated to be the equilibrium structures at the same level of theory. The energetic preference of the inside and anti conformers can be reasonably explained by the stereoelectronic effect, i.e., the gauche effect, on the conformational stability of the ketal moieties.^{22,31}

Regioselectivity in Oxetanes 2 and 3. As found in our previous study on the PB reaction with 2-methylfurane,^{22a} the higher-substituted oxetanes 3 were selectively formed at higher temperatures (Tables 1 and 2). The selective formation of 3 can be understood by the equilibrium constants between the productive inside conformers and the unproductive anticonformers. As exemplified in Scheme 7, the lower-substituted biradicals BR2a and the anticonformers T-BR2a-anti for both the cis and trans-configured biradicals were calculated to be more stable than the productive conformers, T-BR2a-in, by 1.4 kcal/mol at the UB3LYP/6-31+G(d) level of theory. In the higher-substituted

biradicals BR3a, however, the productive conformers, T-BR3a-in, were found to be more stable than the unproductive conformers, T-BR3a-anti. The cis-configured T-BR3a-in was found to be a much more stable conformer than the anticonformer (T-BR3a-anti), since the steric repulsion between the hydroxy group ($R = \text{OH}$, $R' = \text{H}$) and the diphenylmethyl moiety is more severe than that between the hydrogen and the diphenylmethyl group ($R = \text{H}$, $R' = \text{OH}$) in the trans-configured isomer. Thus, the higher population of the inside conformer in the cis-configured biradical, by comparison with the trans-configured one, is a reason for the higher regioselectivity in cis-configured oxetane.

The PB reaction of Allylic Alcohol 4 with BP, Revisited. As found in the PB reaction of 1a,d with BP, the temperature and concentration largely affect the degree of the regioselectivity and diastereoselectivity. The diastereoselectivity of the oxetane formation of 4 with BP also was influenced by the reaction conditions. Thus, the PB reaction was revisited to find the optimal conditions for stereoselectively obtaining oxetane (eq 4), and the results are summarized in Table 4. Actually, diastereoselectivity was largely dependent on the reaction temperature and the concentration of 4. Thus, the diastereoselectivity, threo/erythro, at high temperatures was found to be higher than that at

Scheme 7

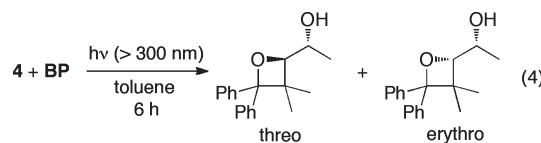


* The energies were relative to the most stable conformer, trans-configured T-BR2a-anti, which were calculated at the UB3LYP/6-31+G(d) level of theory.

low temperature, e.g., 90/10 (entry 2, at 20 °C) and 78/22 (entry 4, −75 °C) at $[4] = 340 \text{ mM}$. This clearly indicates that the hydrogen-bonded aggregation around the hydroxy group decreased diastereoselectivity. Indeed, when the reaction was performed at a higher concentration of **4**, substantial decreases in diastereoselectivity were observed, 54/46 (entry 5) and 65/35 (entry 6). A significant increase in diastereoselectivity was obtained at a lower concentration and reaction temperature (entry 8).

Summary and Conclusions. In the present study, we thoroughly investigated the temperature and concentration effect on regio- and stereoselectivity in the PB reaction of allylic alcohols **1a** and **1d** to clarify the origin of the hydroxy-group directivity in oxetane formation and to provide a reasonable mechanism for a photochemical reaction. In the experimental studies, we found that the selectivities were largely dependent on the reaction conditions due to the existence of the aggregates. At a low concentration of substrate and under high temperature conditions, a cis-selective formation for oxetanes **3a** and **3d** was found. Thus, a hydrogen-bonded interaction together with the steric effect was strongly proposed in the origin of the stereochemical outcome, although hydrogen-bonding stabilization was found to be negligible in the triplet state. The contradiction was solved when the energy profile of the PB reaction of the triplet H_2CO or benzophenone (BP) with **1c** was calculated, in which a clear charge transfer was found from the alkene part to the electron-deficient carbonyl oxygen, leading to the exciplex. The charge transfer makes the carbonyl oxygen nucleophilic, and thus, the oxygen atom becomes the hydrogen-acceptor. The hydrogen-bonded stabilization was actually found in the transition state that produced the cis-configured triplet biradicals. The regioselective formation of the higher-substituted oxetane can be reasonably explained by the equilibrium constant between the productive conformers and the unproductive conformers. The present study gave

Table 4. Temperature and Concentration Effect on the Product Ratios in the PB Reaction of **4 with BP^a**



entry	temp/°C	[4]/mM	products and yields ^b /%		diastereo-selectivity: ^c threo/erythro	mass balance ^d
			threo	erythro		
1	60	340	54	4	88/12	92
2	20	340	67	7	90/10	88
3	−25	340	70	14	88/12	92
4	−75	340	60	17	78/22	88
5	−75	5000	37	31	54/46	90
6	−75	1000	50	27	65/35	86
7	−75	100	62	10	84/16	74
8	−75	6.8	72	3	96/4	77

^a The photoreaction of **4** with benzophenone (BP) was performed in degassed toluene with a high-pressure Hg-lamp through a Pyrex filter. The recovered BP was less than 3% after 6 h of irradiation. Small amounts of compounds **5–7** (~10%) were detected as minor products in the photolysate. ^b The product yields were determined on the basis of ¹H NMR (500 MHz) peak areas (error ±3%). Triphenylmethane (Ph_3CH) was used as an internal standard. ^c The ratios are the normalized threo/erythro stereoselectivity. ^d The values are total yields of **4**, **5–7**, and the recovered BP.

clarity to the poorly understood hydroxy-group directivity of the PB reaction and showed that it is cooperative hydrogen-bonding stabilization and the steric effect that determine selectivity.

■ ASSOCIATED CONTENT

S Supporting Information. Materials list, complete citation for ref 23, NMR spectra for compounds **2** and **3**, NMR spectra for temperature and concentration effects on the product ratios, absolute energies, and optimized Cartesian coordinates. This information is available free of charge via the Internet at <http://pubs.acs.org/>.

■ AUTHOR INFORMATION

Corresponding Author

mabe@hiroshima-u.ac.jp

■ ACKNOWLEDGMENT

NMR and MS measurements were made using JEOL JMN-LA500 and Thermo Fisher Scientific LTD Orbitrap XL spectrometers, respectively, at the Natural Science Center for Basic Research and Development (N-BARD), Hiroshima University. M.A. acknowledges financial support in the form of a Grant-in-Aid for Scientific Research on Innovative Areas “ π -Space” (No 21108516), the Scientific Research (B) (No. 19350021), and Tokuyama Science Foundation.

■ REFERENCES

- (1) (a) Aloisio, S.; Francisco, J. S. *Acc. Chem. Res.* **2000**, *33*, 825–830. (b) Qi, X.-J.; Liu, L.; Fu, Y.; Guo, Q.-X. *Struct. Chem.* **2005**, *16*, 347–353. (c) DeMatteo, M. P.; Poole, J. S.; Shi, X.; Sachdeva, R.; Hatcher, P. G.; Hadad, C. M.; Platz, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 7094–7109. (d) Mardyukov, A.; Sanchez-Garcia, E.; Crespo-Otero, R.; Sander, W. *Angew. Chem., Int. Ed.* **2009**, *48*, 4804–4807. (e) Hammeru, S. *J. Am. Chem. Soc.* **2009**, *131*, 8627–8635. (f) Mitroka, S.; Zimmeck, S.; Troya, D.; Tanko, J. M. *J. Am. Chem. Soc.* **2010**, *132*, 2907–2913. (g) Mardyukov, A.; Crespo-Otero, R.; Sanchez-Garcia, E.; Sander, W. *Chem.—Eur. J.* **2010**, *16*, 8679–8689. (h) Muthukrishnan, S.; Sankaranarayanan, J.; Pace, T. C. S.; Konosonoks, A.; DeMichiei, M. E.; Meese, M. J.; Bohne, C.; Gudmundsdottir, A. D. *J. Org. Chem.* **2010**, *75*, 1393–1401.
- (2) (a) Jeffrey, G. A. In *An Introduction to Hydrogen-Bonding*; Oxford University Press: New York, 1997. (b) Steiner, T. *Angew. Chem., Int. Ed.* **2002**, *41*, 48–76.
- (3) (a) Johnson, R. A.; Sharpless, K. B. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, 1993; Chapter 4.1 (b) Adam, W.; Wirth, T. *Acc. Chem. Res.* **1999**, *32*, 703–710. (c) Tripathy, R.; Carroll, P. J.; Thornton, E. R. *J. Am. Chem. Soc.* **1990**, *112*, 6743–6744. (d) Pearson, R. J.; Kassianidis, E.; Philp, D. *Tetrahedron Lett.* **2004**, *45*, 4777–4780. (e) Narayan, S.; Muldoon, J.; Finn, M. G.; Fokin, V. V.; Kolb, H. C.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2005**, *44*, 3275–3279.
- (4) The importance of hydrogen-bonding in photochemical reactions, see: (a) Bauer, A.; Westkaemper, F.; Grimme, S.; Bach, T. *Nature* **2005**, *436*, 1139–1140. (b) Yokoyama, A.; Mizuno, K. *Org. Lett.* **2000**, *2*, 3457–3459. (c) Bach, T.; Bergmann, H.; Harms, K. *J. Am. Chem. Soc.* **1999**, *121*, 10650–10651. (d) Sieburth, S. McN.; McGee, K. F., Jr. *Org. Lett.* **1999**, *1*, 1775–1777. (e) Sydnes, L. K.; Hansen, K. I.; Oldroyd, D. L.; Weedon, A. C.; Jorgensen, E. *Acta Chem. Scand.* **1993**, *47*, 916–924. (f) Hoffmann, N. *Chem. Rev.* **2008**, *108*, 1052–1103.
- (5) Ng, S. M.; Bader, S. J.; Snapper, M. L. *J. Am. Chem. Soc.* **2006**, *128*, 7315–7319.
- (6) (a) Paternò, E.; Chieffi, G. *Gazz. Chim. Ital.* **1909**, *39* (I), 341–361. (b) Büchi, G.; Inman, C. G.; Lipinsky, E. S. *J. Am. Chem. Soc.* **1954**, *76*, 4327–4331. (c) Yang, N. C.; Nussim, M.; Jorgenson, M. J.; Murov, S. *Tetrahedron Lett.* **1964**, *5*, 3657–3664. (d) Arnold, D. R. *Adv. Photochem.* **1968**, *6*, 301–349. (e) Carless, H. A. *Synthetic Organic Photochemistry*; Horspool, W. M., Ed.; Plenum Press: New York, 1984; p 425–487. (f) Griesbeck, A. G. *CRC Handbook of Organic Photochemistry and Photobiology*; Horspool, W. M., Song, P.-S., Eds.; CRC Press: Boca Raton, FL, 1994; pp 522–535 and 536–549. (g) Griesbeck, A. G.; Bondock, S. *CRC Handbook of Organic Photochemistry and Photobiology*, 2nd ed.; Horspool, W. M.; Lenci, F., Eds.; CRC Press: Boca Raton, FL, 2004; Chapters 59 and 60. (h) Abe, M. *CRC Handbook of Organic Photochemistry and Photobiology*, 2nd ed.; Horspool, W. M.; Lenci, F., Eds.; CRC Press: Boca Raton, FL, Chapter 62. (i) Porco, J. A.; Schreiber, S. L. *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 5, pp 151–192. (j) Bach, T. *Liebigs Ann.* **1997**, 1627–1634. (k) Bach, T. *Synthesis* **1998**, 683–703.
- (7) (a) Adam, W.; Peters, K.; Peters, E. M.; Stegman, V. R. *J. Am. Chem. Soc.* **2000**, *122*, 2958–2959. (b) Adam, W.; Stegmann, V. R. *Synthesis* **2001**, 1203–1214. (c) D’Auria, M.; Racioppi, R.; Romaniello, G. *Eur. J. Org. Chem.* **2000**, 3265–3272. (d) D’Auria, M.; Emanuele, L.; Poggi, G.; Racioppi, R.; Romaniello, G. *Tetrahedron* **2002**, *58*, 5045–5051. (e) D’Auria, M.; Emanuele, L.; Racioppi, R. *Photochem. Photobiol. Sci.* **2004**, *3*, 927–932. (f) D’Auria, M.; Emanuele, L.; Racioppi, R.; Valente, A. *Photochem. Photobiol. Sci.* **2008**, *7*, 98–103.
- (8) Wolf, M. W.; Brown, R. E.; Singer, L. A. *J. Am. Chem. Soc.* **1977**, *99*, 526–531.
- (9) Zimmerman, H. E. *Angew. Chem., Int. Ed.* **1969**, *8*, 1–11.
- (10) Paul, H.; Small, R. D., Jr.; Scaiano, J. C. *J. Am. Chem. Soc.* **1978**, *100*, 4520–4527.
- (11) (a) Scaiano, J. C. *J. Photochem.* **1973**, *2*, 81–118. (b) Rao, C. N. R.; Murthy, A. S. N. *Theoret. Chim. Acta* **1971**, *22*, 392–395. (c) Del Bene, J. E. *J. Am. Chem. Soc.* **1973**, *95*, 6517–6522. (d) Del Bene, J. E.; Gwaltney, S. R.; Bartlett, R. J. *J. Phys. Chem. A* **1998**, *102*, 5124–5127. (e) Del Bene, J. E.; Watts, J. D. *Int. J. Quan. Chem.* **2000**, *77*, 187–191. (f) Pischel, U.; Nau, W. M. *Photochem. Photobiol. Sci.* **2002**, *1*, 141–147.
- (12) (a) Morokuma, K. *J. Chem. Phys.* **1971**, *55*, 1236–1244. (b) Iwata, S.; Morokuma, K. *Chem. Phys. Lett.* **1973**, *19*, 94–98. (c) Iwata, S.; Morokuma, K. *J. Am. Chem. Soc.* **1973**, *95*, 7563–7575.
- (13) (a) Liao, D.-W.; Mebel, A. M.; Chen, Y.-T.; Lin, S.-H. *J. Phys. Chem. A* **1997**, *101*, 9925–9934. (b) Wagner, P. J.; Truman, R. J.; Scaiano, J. C. *J. Am. Chem. Soc.* **1985**, *107*, 7093–7097. (c) Wagner, P. J.; Park, B.-S. In *Organic Photochemistry*; Padwa, A., Ed.; Marcel Dekker: New York, 1991; Vol. 11, Chapter 4.
- (14) (a) Ciamician, G.; Silber, P. *Chem. Ber.* **1900**, *33*, 2911–2913. (b) Jacques, P. *J. Photochem. Photobiol. A: Chem.* **1991**, *56*, 159–163.
- (15) Griesbeck, A. G.; Bondock, S. *J. Am. Chem. Soc.* **2001**, *123*, 6191–6192.
- (16) (a) Abe, M.; Terazawa, M.; Nozaki, K.; Masuyama, A.; Hayashi, T. *Tetrahedron Lett.* **2006**, *47*, 2527–2530. (b) Yabuno, Y.; Hiraga, Y.; Abe, M. *Chem. Lett.* **2008**, 822–823.
- (17) *Chiral Photochemistry*; Inoue, Y.; Ramamurthy, V., Eds.; Marcel Dekker: New York, 2004.
- (18) In our previous study (ref 16b), only the temperature effect on selectivity was examined in the PB reaction of **1a** with benzophenone. The concentration effect was also investigated in the present study to clarify the effect of the aggregation on the regio- and stereoselectivity (Scheme 1).
- (19) The conformation of the intermediary triplet biradical is important in controlling the stereoselectivity in the PB reactions, i.e., Griesbeck model: (a) Griesbeck, A. G.; Stadtmüller, S. *J. Am. Chem. Soc.* **1990**, *112*, 1281–1288. (b) Griesbeck, A. G.; Stadtmüller, S. *J. Am. Chem. Soc.* **1991**, *113*, 6923–6928. (c) Griesbeck, A. G.; Mauder, H.; Stadtmüller, S. *Acc. Chem. Res.* **1994**, *27*, 70–75. (d) Abe, M.; Torii, E.; Nojima, M. *J. Org. Chem.* **2000**, *65*, 3426–3431. (e) Abe, M.; Fujimoto, K.; Nojima, M. *J. Am. Chem. Soc.* **2000**, *122*, 4005–4010. (f) Abe, M.; Taniguchi, K. *ARKIVOC* **2007**, 58–65. (g) Hei, X. M.; Song, Q. H.; Li, X. B.; Tang, W. J.; Wang, H. B.; Guo, Q. X. *J. Org. Chem.* **2005**, *70*, 2522–2527.
- (20) (a) Lee, M.; Moritomo, H.; Kanematsu, K. *Tetrahedron* **1996**, *52*, 8169–8180. (b) Lautens, M.; Fillion, E. *J. Org. Chem.* **1997**, *62*, 4418–4427.
- (21) (a) Head-Gordon, M.; Pople, J. A.; Frisch, M. J. *Chem. Phys. Lett.* **1988**, *153*, 503–506. (b) Saebo, S.; Almlöf, A. *Chem. Phys. Lett.*

1989, 154, 83–89. (c) Frisch, M. J.; Head-Gordon, M.; Pople, J. A. *Chem. Phys. Lett.* **1990**, 166, 275–280. (d) Frisch, M. J.; Head-Gordon, M.; Pople, J. A. *Chem. Phys. Lett.* **1990**, 166, 281–289. (e) Head-Gordon, M.; Head-Gordon, T. *Chem. Phys. Lett.* **1994**, 220, 122–128.

(22) (a) Hariharan, P. C.; Pople, J. A. *Theor. Chim. Acta* **1973**, 28, 213–222. (b) Becke, A. D. *J. Chem. Phys.* **1993**, 98, 5648–5652. (c) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, 37, 785–789. (d) Foresman, J. B.; Head-Gordon, M.; Pople, J. A.; Frisch, M. J. *J. Phys. Chem.* **1992**, 96, 135–149.

(23) Frisch, M. J. et al. Gaussian 03, Revision C.02, Gaussian Inc.: Wallingford, CT, 2004.

(24) (a) Abe, M.; Kawakami, T.; Ohata, S.; Nozaki, K.; Nojima, M. *J. Am. Chem. Soc.* **2004**, 126, 2838–2846. (b) Griesbeck, A. G.; Abe, M.; Bondock, S. *Acc. Chem. Res.* **2004**, 37, 919–928. (c) Abe, M. *J. Chin. Chem. Soc. (Taipei)* **2008**, 55, 479–486. (d) Abe, M. In *Handbook of Synthetic Photochemistry*; Albini, A., Fagnoni, M., Eds.; Wiley-VCH, Weinheim, 2010, 217–239.

(25) A-factor of OH (solvent), 0.60 (C_6H_{12}) and 0.95 ($CH_3CHOHCH_3$): Eliel, E. L.; Wilen, S. H. In *Stereochemistry of Organic Compounds*; John Wiley & Sons: New York, 1994; pp 696–697.

(26) A PB reaction of benzophenone with the methyl ether of 2-furylmethanol was reported to produce no oxetane formation; see ref 7c.

(27) Zimmerli, U.; Parrinello, M.; Koumoutsako, P. *J. Chem. Phys.* **2004**, 120, 2693–2699.

(28) Triplet 1,4-biradicals are the common intermediate in the PB reaction of the electron rich alkenes: (a) Freilich, S. C.; Peters, K. S. *J. Am. Chem. Soc.* **1981**, 103, 6255–6257. (b) Freilich, S. C.; Peters, K. S. *J. Am. Chem. Soc.* **1985**, 107, 3819–3822. (c) Palmer, I. J.; Ragazos, I. N.; Barbardi, F.; Olivucci, M.; Robb, M. A. *J. Am. Chem. Soc.* **1994**, 116, 2121–2132.

(29) Matsumura, K.; Mori, T.; Inoue, Y. *J. Org. Chem.* **2010**, 75, 5461–5469.

(30) Kutateladze, A. G. *J. Am. Chem. Soc.* **2001**, 123, 9279–9282.

(31) In *The Anomeric Effect and Associated Stereoelectronic Effects*; ACS Symposium Series 539; Thatcher, G. R. J., Ed.; American Chemical Society: Washington, DC, 1993.