Site- and Stereoselectivity in the Photochemical Oxetane Formation Reaction (Paternò–Büchi Reaction) of Tetrahydrobenzofuranols with Benzophenone: Hydroxy-directed Diastereoselectivity?

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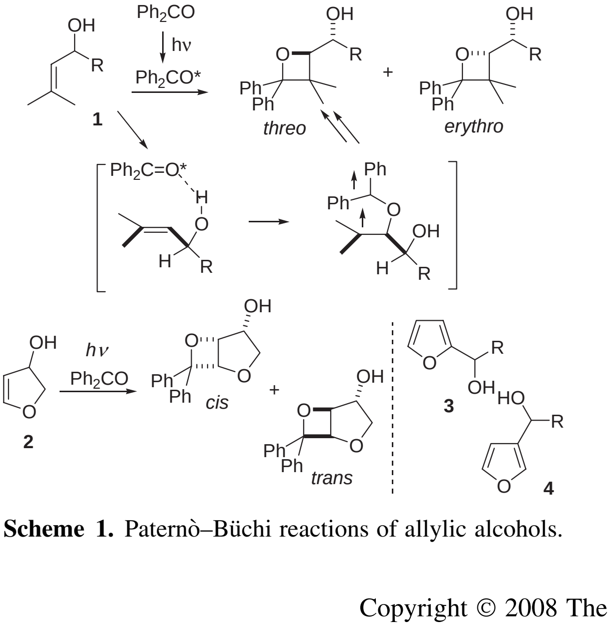
The Paternò–Büchi reactions of tetrahydrobenzofuranols with benzophenone were investigated to reveal site- and stereoselectivity in oxetane formation reactions. Both selectivities were found to be largely dependent on the reaction temperature. The trans selectivity increased with a decrease in temperature, and the more-substituted oxetanes were selectively formed at high temperature.

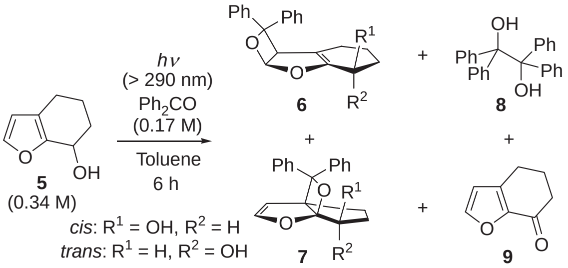
The photochemical [2 + 2] cycloaddition reaction of carbonyl compounds with alkenes, the so-called Paternò–Büchi (PB) reaction,[1] is the most versatile method for preparing oxetane derivatives, which are synthetically and biologically important.[2] Although the reaction involves an energized species, i.e. an electronically excited carbonyl group (RCO*), regio-, site-, and stereoselective formation of oxetanes have been achieved within the past two decades. In 2000, a threo-selective formation of oxetanes was found in the PB reaction of benzophenone (Ph_2CO^*) with allylic alcohols **1** (Scheme 1).[3] The diastereofacial selectivity was explained by the hydrogen-bonding interaction[4] between the hydroxy group and the incoming molecule, Ph_2CO^*. On the other hand, it has shown that the reactive n, π^* excited carbonyl is a very electron-deficient species.[5] We found that a trans-selective formation of the bicyclic oxetane in the PB reaction cyclic allylic alcohol **2** in low temperature (Scheme 1).[6] The trans selectivity is apparently not consistent with hydroxy-directed diastereoselectivity, i.e. cis selectivity. In the PB reaction of furyl alcohols **3** and **4**, the hydroxy-directed site- and stereoselective formation of oxetanes was postulated to be important in controlling the site- and diastereoselectivity.[7] Although site-selectivity (double-bond selection) in a PB reaction of furans is known to be largely dependent on reaction temperature,[8] the temperature effect on the selectivity was not examined in the literatures.[7] Thus, thorough verification of "hydroxy-directivity" is needed in PB reactions of furan derivatives. The purpose of this study is to clarify the site- and diastereofacial selectivity of the oxetane formation in the PB reaction of benzophenone with tetrahydrobenzofuran-7-ol (**5**) (Table 1) and with tetrahydrobenzofuran-4-ol (**10**) (Table 2). The intent was to determine how the hydroxy group and its position on the ring system affect site- and diastereoselectivity. In this study, the selectivities were found to be largely dependent on the reaction temperature, and not significantly affected by the position of the hydroxy group. This implies that "hydroxy-directed selectivity" is not always applicable for predicting the diastereoselectivity of photochemical oxetane formation reactions of allylic alcohols.



Scheme 1. Paternò–Büchi reactions of allylic alcohols.

The experimental results of the photochemical reaction of **5** are summarized in Table 1. Bicyclic oxetanes **6** and **7** were isolated and fully characterized by spectroscopic analyses.[9] The cis and trans configurations were unambiguously determined using ^{1}H NMR NOE measurement.[9] Both isomers were stable under irradiation conditions, and the ratios did not change. The pinacol **8** and the oxidation product **9** were also detected as minor products in the photochemical reaction. The mass balances of the photochemical reactions were quite high both in toluene (Entries 1–5) and in DMSO (Entry 6), >84%. As found in the reaction with allylic alcohol **2**, the trans selectivity in bicyclic oxetanes **6** and **7** increased with a decrease in temperature. Thus, the trans selectivity observed in the PB reaction of **5** at low temperature may not be explained by hydroxy-directed effect (Entries 3–5). The site-selectivity, **6** vs. **7**, was also largely dependent on the reaction temperature. Thus, the more-substituted oxetane **7** was selectively formed at high temperature, and the chemical yield of less-substituted oxetane **6** increased with a decrease in temperature, e.g. **6**/**7** = 14/86 at 60 °C (Entry 1) and **6**/**7** = 45/55 at −75 °C (Entry 5). The temperature effect on the site-selectivity was quite similar to the case of the PB reaction of unsymmetrically substituted furan derivatives.[8] When the PB reaction was carried out in an aprotic polar-solvent, DMSO, the highly trans selective formation of oxetanes **6** and **7** was observed (Entry 6), i.e. *cis*/*trans*-**6**,**7** < 3/97. This result implies that the steric factor plays an important role in controlling diastereofacial selectivity. Thus, the hydrogen-bonded DMSO molecules would increase the size of the steric hindrance of the hydroxy group. Next, we investigated the site- and diastereoselectivity in the PB reaction of tetrahydrobenzofuran-4-ol

Table 1. Temperature effect on the site- and stereoselectivity of bicyclic oxetanes in the Paternò–Büchi reaction of **5**[a]



Entry	Temp /°C	Products and yields[b]/%			
		6 cis/trans	**7** cis/trans	**8**	**9**
1	60	3/7	37/28	6	3
2	20	4/12	36/30	3	2
3	−25	5/23	28/36	2	2
4	−46	7/28	23/39	2	2
5	−75	7/31	13/33	2	1
6[c]	20	<3/20	<3/44	7	11

[a] The photoreaction was conducted as follows: a degassed solution of **5** (0.34 M) and Ph_2CO (0.17 M) was irradiated for 6 h with a high-pressure Hg lamp (300 W) through a Pyrex filter. The conversion of benzophenone was almost 100%. [b] The yields were determined by ^{1}H NMR (500 MHz) peak areas; Ph_3CH was used as an internal standard; error ±3%. [c] DMSO was used as solvent.

(**10**) with benzophenone under similar irradiation conditions (Table 2). Unfortunately, less-substituted oxetane **11** is moisture-sensitive, and thus, was labile under the isolation conditions (silica gel) to give the aldehyde **12**. The cis and trans isomer of the more-substituted oxetane **13** were isolated and fully characterized by spectroscopic analyses. The configurational determination was unambiguously confirmed by conventional NOE measurements.[9] Although the diastereoselectivity in the formation of oxetane **11** could not be determined, trans selectivity was again observed in the formation of the more-substituted oxetane **13** at low temperature (Entry 3 in Table 2). The temperature-dependent change of the diastereoselectivity was quite similar to that observed in the PB reaction of **5**; for *cis*/*trans*-**13** = 58/42 (60 °C) and 24/76 (−75 °C), for *cis*/*trans*-**7** = 57/43 (60 °C) and 28/72 (−75 °C). As found for the reaction of **5** (Table 1), the site-selectivity, **12** (=**11**) versus **13**, was also largely dependent on the reaction temperature. Thus, the site- and stereoselectivity observed in the PB reactions were not largely dependent on the position of the hydroxy group in the tetrahydrobenzofuranols. In this study, we found that the site- and stereoselectivity of the oxetane formation in the PB reactions of **5** and **10** were largely dependent on the reaction temperature, and not so significantly influenced by the position of the hydroxy group. Thus, diastereoselectivity in the formation of oxetanes derived from allylic alcohols may not be simply predicted by just the "hydroxy-directed effect." This remarkable finding should stimulate future calculations and experiments on the mechanistically fascinating temperature effects of site- and stereoselectivity in oxetane formation reactions.

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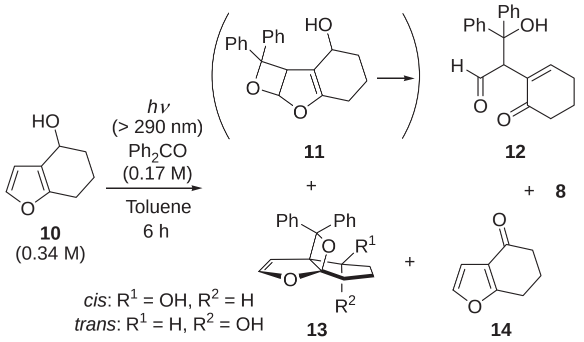
Table 2. Temperature effect on the site- and stereoselectivity of bicyclic oxetanes in the Paternò–Büchi reaction of **10**[a]



Entry	Temp /°C	Products and yields[a]/%			
		12 (=**11**)	**13** cis/trans	**8**	**14**
1	60	6	31/22	9	7
2	20	19	30/23	9	5
3	−75	23	9/29	9	3

[a] The photoreaction was conducted under the similar conditions for **5**, see footnote of Table 1. The conversion of benzophenone was 96% (Entry 1), 83% (Entry 2), and 75% (Entry 3), respectively.

References and Notes

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9 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.