

# Hydroxy Group-directed Diastereoselective Paterno-Buchi Reaction between Arylglyoxylates and Furfuryl Alcohols

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| journal or publication title | Chemistry Letters   |
| volume                       | 51  |
| number                       | 12  |
| page range                   | 1143-1145   |
| year                         | 2022-12-05  |
| URL                          | <a href="http://doi.org/10.24517/00068484">http://doi.org/10.24517/00068484</a> |

doi: 10.1246/cl.220437



## Hydroxy Group-Directed Diastereoselective Paternò-Büchi Reaction between Arylgyoxylates and Furfuryl Alcohols

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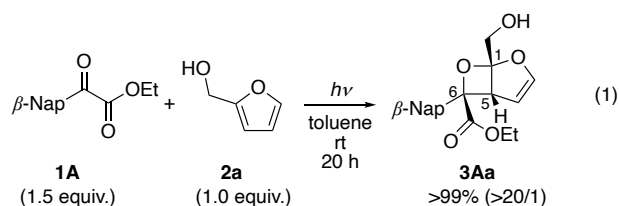
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1 A hydroxy group-directed Paternò-Büchi (PB) reaction  
2 between arylglyoxylates and furfuryl alcohols afforded the  
3 corresponding oxetanes regio- and diastereoselectively.  
4 Furthermore, the PB reaction between  $\beta$ -naphthylglyoxylate  
5 possessing diisopropyl (*R,R*)-tartrate moiety and furfuryl  
6 alcohol achieved high chiral induction to produce the  
7 corresponding optically pure oxetane after the removal of the  
8 chiral auxiliary.

9 **Keywords:** Paternò-Büchi Reaction, Directing Group,  
10 Oxetane  
11

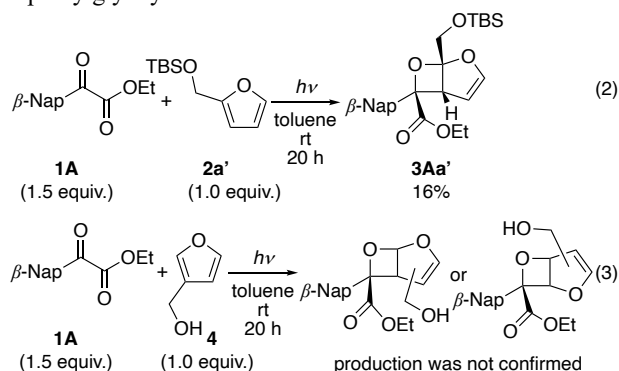
12 Paternò-Büchi (PB) reaction, the [2+2]  
13 photocycloaddition reaction between a carbonyl compound  
14 and an alkene, is one of the most efficient ways to synthesize  
15 functionalized oxetanes.<sup>1</sup> With the help of the PB reaction,  
16 various oxetanes have been produced for accessing  
17 biologically active natural and unnatural compounds.<sup>2</sup>  
18 Hydrogen bonding has been reported to control the  
19 stereochemical course in the photochemical cycloaddition  
20 including the PB reaction.<sup>3,4</sup> Initially, Adam and Griesbeck  
21 reported that allylic alcohols react with aromatic carbonyl  
22 compounds to afford the corresponding oxetanes with high  
23 regio- and diastereoselectivity.<sup>3b-3d</sup> PB reaction using furfuryl  
24 alcohol derivatives was studied in detail by Abe and D' Auria,  
25 and hydrogen bonding interaction was reported to be  
26 effective in controlling the stereochemical course.<sup>1c,1e,1f,1h,3e,4</sup>  
27 However, the regio- and diastereoselectivities, as well as the  
28 chemical yields, were not always high enough, and there is  
29 still room for improvement of stereoselectivities and  
30 chemical yields. In our study on photoreactions using allylic  
31 alcohol derivatives,<sup>5</sup> we were interested in furfuryl alcohol as  
32 a particular type of allylic alcohol toward the PB reaction.  
33 Among the carbonyl compounds,  $\alpha$ -keto esters are promising  
34 because of their potential to form hydrogen bondings.<sup>6</sup> Herein,  
35 we report a stereoselective hydroxy group-directed PB  
36 reaction between arylglyoxylates and furfuryl alcohols.<sup>7</sup>  
37 Furthermore, chiral induction was observed in the PB  
38 reaction of  $\beta$ -naphthylglyoxylate with tartaric acid moiety.

39 In this study, ethyl  $\beta$ -naphthylglyoxylate (**1A**) was used  
40 for the PB reaction with furfuryl alcohol (**2a**). The reaction  
41 between **1A** (1.5 equiv.) and **2a** proceeded in toluene under  
42 light<sup>8</sup> at room temperature, to afford the corresponding  
43 oxetane **3Aa** with a quantitative yield and diastereoselectivity  
44 of >20/1 (eq. 1).<sup>9,10</sup> Regioisomers were not observed in the <sup>1</sup>H  
45 NMR spectra of the crude products.<sup>7</sup> The structure and  
46 relative stereochemistry of **3Aa** were confirmed to be  
47 1*R*\*,5*R*\*,6*R*\* by X-ray crystallographic analysis.<sup>11</sup>



48

49 To clarify the role of the hydroxy group, *t*-  
50 butyldimethylsilyl ether of furfuryl alcohol **2a'** was subjected  
51 to the PB reaction with  $\beta$ -naphthylglyoxylate **1A**. The  
52 reaction was quite sluggish, giving the corresponding oxetane  
53 **3Aa'** with a 16% yield (eq. 2). Furthermore, the PB reaction  
54 of 3-furanmethanol (**4**) with **1A** was also examined.<sup>12</sup>  
55 However, most of **1A** and **4** were recovered and the  
56 production of chemicals containing both  $\beta$ -naphthyl and  
57 hydroxymethyl moieties could not be confirmed after  
58 purification by silica gel column chromatography (eq. 3).  
59 These results indicate that the hydroxy group in furfuryl  
60 alcohol (**2a**) is crucial to the reactivity, in addition to the  
61 regio- and diastereoselectivities of the PB reaction of  $\beta$ -  
62 naphthylglyoxylate.  
63

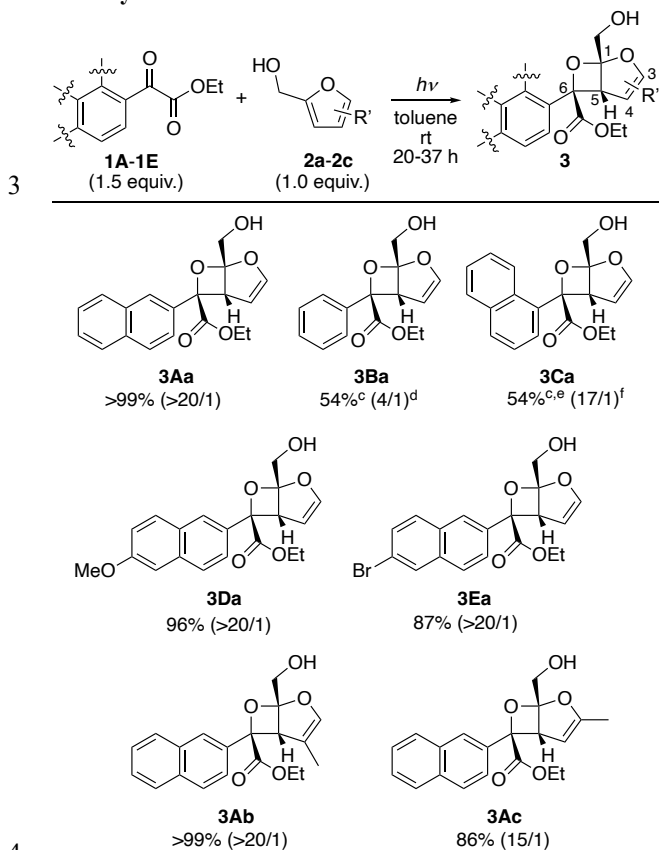


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65

66 Several PB reactions between arylglyoxylates and  
67 furfuryl alcohols were examined as listed in Table 1.<sup>10</sup> The  
68 PB reaction of ethyl phenylglyoxylate (**1B**) was slightly  
69 sluggish. When 3 equiv. (based on **1B**) of furfuryl alcohol  
70 (**2a**) were used, the corresponding oxetane **3Ba** was obtained  
71 in 44% yield, along with a diastereomer yield of 10%. Ethyl  
72  $\alpha$ -naphthylglyoxylate (**1C**) was also slightly unreactive, and  
73 cycloadduct **3Ca** was obtained in 54% yield  
74 diastereoselectively when 3 equiv. of **2a** (based on **1C**) was  
75 used. The introduction of electron-donating and electron-  
76 withdrawing groups at the 6-position of the naphthalene ring  
77 did not affect to furnish the corresponding oxetanes **3Da** and  
78 **3Ea** in high yields and diastereoselectivities. The PB  
79 reactions of 4-methyl- and 5-methyl-substituted furfuryl  
80 alcohols **2b** and **2c** were carried out to achieve excellent  
81 diastereoselectivities.

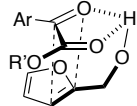
1 **Table 1. Paternò–Büchi Reaction of Aryl glyoxylates **1** and**  
 2 **Furfuryl Alcohols **2****<sup>a,b</sup>



6 <sup>a</sup>Isolated yields of a mixture of (1*R*\*,5*R*\*,6*R*\*)-**3** and  
 7 (1*R*\*,5*R*\*,6*S*\*)-isomers are listed. <sup>b</sup>The (1*R*\*,5*R*\*,6*R*\*)-  
 8 **3**/(1*R*\*,5*R*\*,6*S*\*)-isomer diastereomeric ratios were  
 9 determined based on the <sup>1</sup>H NMR signals of the substituents  
 10 (H or CH<sub>3</sub> in the case of **3Ac**) on vinylic C3. <sup>c</sup>One equiv. of  
 11 **1** and 3 equiv. of **2a** were used. <sup>d</sup>Yield and diastereomeric  
 12 ratio were determined by isolation of both (1*R*\*,5*R*\*,6*R*\*)-  
 13 **3Ba** and (1*R*\*,5*R*\*,6*S*\*)-isomer. <sup>e</sup>The isolated yield of  
 14 (1*R*\*,5*R*\*,6*R*\*)-**3Ca**. <sup>f</sup>Diastereomeric ratio was determined  
 15 based on the <sup>1</sup>H NMR signals of the crude products.

16 Although the exact  
 17 mechanism of the present PB  
 18 reaction is not clear, a model  
 19 for the diastereoselection  
 20 could be proposed as depicted  
 21 in Figure 1 based on the  
 22 confirmed relative  
 23 stereochemistry of the obtained cycloadduct.<sup>11</sup> The  
 24 conformation of  $\alpha$ -keto ester **1** is fixed to *s-cis* by the  
 25 hydrogen bonding between the hydroxy group of furfuryl  
 26 alcohol **2** to afford (1*R*\*,5*R*\*,6*R*\*)-**3** stereoselectively.<sup>13</sup>

27 The possibility of chiral induction in the PB reaction by  
 28 hydrogen bonding was investigated as shown in Table 2.<sup>14</sup> An  
 29 ester **5A** derived from  $\beta$ -naphthylglyoxylic acid and (*R,R*)-  
 30 diethyl tartrate was used as the substrate. When **5A** was  
 31 treated with furfuryl alcohol (**2a**), the PB reaction proceeded



32 **Figure 1. Proposed Model**  
 33 **for Diastereoselection**

32 smoothly to give the corresponding oxetane **6A**. The  
 33 diastereomeric ratio was determined to be 8/1 by <sup>1</sup>H NMR  
 34 analysis.<sup>15</sup> The effect of the ester group in the tartrate moiety  
 35 was found to slightly affect the diastereoselectivity, and the  
 36 corresponding isopropyl ester **6C** achieved 10/1 selectivity.

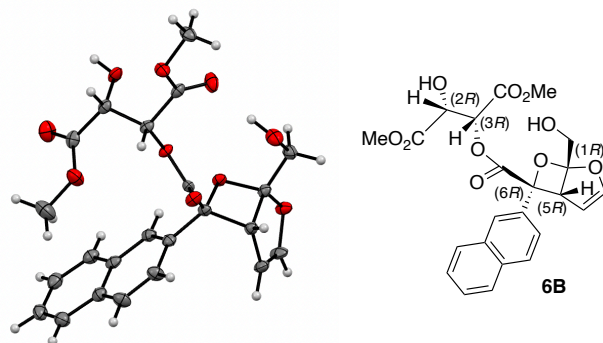
37  
 38 **Table 2. Chiral Induction in Paternò–Büchi Reaction of**  
 39  **$\beta$ -Naphthylglyoxylates **5** with Tartaric Acid Moiety**

40

| Entry | R            | <b>5,6</b> | Yield/% <sup>a</sup> | Diastereomeric ratio <sup>b</sup> |
|-------|--------------|------------|----------------------|-----------------------------------|
| 1     | Et           | <b>A</b>   | 81                   | 8/1 <sup>c</sup>                  |
| 2     | Me           | <b>B</b>   | 84                   | 8/1 <sup>d</sup>                  |
| 3     | <i>i</i> -Pr | <b>C</b>   | 91                   | 10/1 <sup>c</sup>                 |
| 4     | <i>t</i> -Bu | <b>D</b>   | 91                   | 8/1 <sup>d</sup>                  |

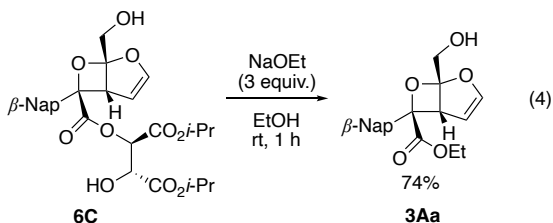
41 <sup>a</sup>Isolated yields of a mixture of (1*R*,5*R*,6*R*)-**6** and (1*S*,5*S*,6*S*)-  
 42 isomer are listed. <sup>b</sup>The (1*R*,5*R*,6*R*)-/(1*S*,5*S*,6*S*)-isomer  
 43 diastereomeric ratios were listed. <sup>c</sup>Diastereomeric ratio was  
 44 determined based on the <sup>1</sup>H NMR signals of protons on the  
 45 vinylic C4. <sup>d</sup>Diastereomeric ratio was determined based on  
 46 the <sup>1</sup>H NMR signals of C3 protons in the tartaric acid moiety.

47  
 48 The stereochemistry of the oxetane skeleton in the major  
 49 isomer of **6B** was determined to be 1*R*,5*R*,6*R* by X-ray  
 50 crystallographic analysis of its single crystal (Figure 2). The  
 51 putative stereochemistry of oxetane moieties in other  
 52 products **6A**, **6C**, and **6D** with the (*R,R*)-tartaric acid moiety  
 53 was also 1*R*,5*R*,6*R*.



54 **Figure 2. X-ray Structure of **6B**** (Flack parameter: 0.09(4))

55  
 56  
 57 The tartrate moiety was readily removed from  
 58 diastereomerically pure **6C** by treatment with NaOEt to  
 59 afford optically pure oxetane **3Aa** (eq. 4).



In conclusion, we developed a hydroxy-group-directed stereoselective PB reaction between arylglyoxylates and furfuryl alcohols. The optically active oxetane was successfully synthesized via the diastereoselective PB reaction of glyoxylate with a tartaric acid ester moiety. This study provides an excellent example of stereochemical control in the PB reaction by hydrogen bonding. The stereoselective formation of highly oxygenized oxetanes can potentially be used for the synthesis of biologically active compounds containing oxetane rings.<sup>2</sup>

This work was partially supported by Grants-in-Aid from the Japan Society for the Promotion of Science.

Supporting Information is available on [http://dx.doi.org/10.1246/cl.\\*\\*\\*\\*\\*](http://dx.doi.org/10.1246/cl.*****).

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hindered side of **2a**: M. D'Auria, L. Emanuele, R. Racioppi, *Photochem. Photobiol. Sci.* **2003**, *2*, 904.

All photoreactions were carried out by irradiation with ca. 340–520 nm light using 450 W high-pressure mercury lamp (Ushio UM-452 or Sen HL450EH-3) in a Pyrex vessel through an aqueous CuSO<sub>4</sub> filter. See, S. L. Murov, in *Handbook of Photochemistry*, Dekker, Inc. New York, **1973**, p. 317.

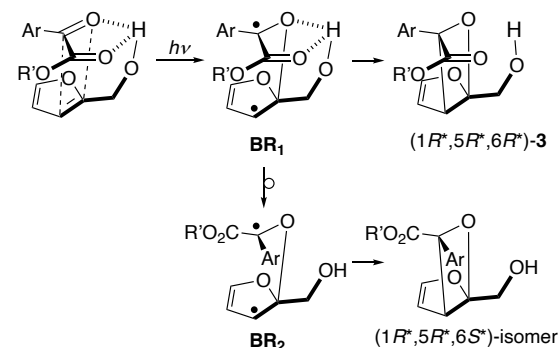
Brief optimization of reaction conditions is shown in Table S1 in Supporting Information.

Minor products were considered to be diastereomers (1*R*\*,5*R*\*,6*S*\*)-**3**: See Supporting Information.

X-ray analytical data and ORTEP were shown at Figure S1 in Supporting Information.

PB reaction to 3-furanmethanol derivatives: M. D'Auria, L. Emanuele, R. Racioppi, A. Valente, *Photochem. Photobiol. Sci.* **2008**, *7*, 98.

It is not clear yet why the diastereoselectivities differed among the substituents Ar. PB reaction is proposed to often proceed through 1,4-biradical intermediate via an initial C–O bond formation.<sup>1</sup> In the present research, the oxetane rings might be produced through the initially formed biradical intermediate **BR**<sub>1</sub>. One reason for the lower diastereoselectivity in the case of **1B** (Ar = Ph) might be ascribed to the differences of steric hindrance of the substituents. That is, rotation about the C<sub>benzylic</sub>–O bond occurs to give the minor (1*R*\*,5*R*\*,6*S*\*)-isomer through **BR**<sub>2</sub> in the case of less sterically hindered phenyl group. In the case of **5** described below in Table 2, the bulkiness of tartrate moiety (OR') might further retard the C<sub>benzylic</sub>–O bond rotation to avoid the production of (1*R*,5*R*,6*S*)- and (1*S*,5*S*,6*R*)-isomers more completely.



Diastereoselective PB reaction of arylglyoxylates possessing chiral auxiliaries: a) H. Buschmann, H.-D. Scharf, N. Hoffmann, P. Esser, *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 477. b) K. Terao, Y. Nishiyama, K. Kakiuchi, *J. Flow Chem.* **2014**, *4*, 35 and refs. 1h and 7.

The diastereomers of the oxetane ring (1*R*,5*R*,6*S*)- and (1*S*,5*S*,6*R*)-isomers were not detected. The minor products were assigned as (1*S*,5*S*,6*S*)-isomers bearing a (2*R*,3*R*)-tartaric acid skeleton (see Supporting Information).

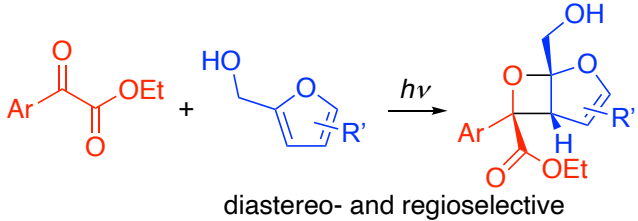
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| Textual Information  |   |
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| Title(required)  | Hydroxy Group-Directed Diastereoselective Paternò-Büchi Reaction between Arylglyoxylates and Furfuryl Alcohols  |
| Authors' Names(required)   | Qi Wei, Hiromi Ii, Takuya Suga, Takahiro Soeta, Hajime Maeda, and Yutaka Ukaji*   |
| Graphical Information  |   |
|  <p style="text-align: center;">diastereo- and regioselective</p> |   |
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