

## Hydroxy-Directed Regio- and Diastereoselective [2+2] Photocycloaddition (Paternò–Büchi Reaction) of Benzophenone to Chiral Allylic Alcohols

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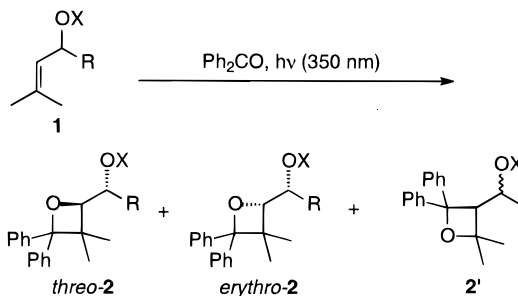
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Chiral allylic alcohols with 1,3-allylic strain have attracted much attention due to their stereodirecting propensity in diastereoselective reactions; indeed, they have proved to be valuable substrates, from both the synthetic and mechanistic point of view.<sup>1</sup> In all of the established examples, the combined action of 1,3-allylic strain in the allylic alcohol and the hydrogen bonding between the allylic hydroxy group and the reaction partner is the common controlling feature to achieve high diastereoselectivities and enhance the regioselectivity. Thus, as the consequence of the hydroxy-group directivity, all three pericyclic reaction modes of the photooxygenation, namely the ene reaction<sup>2</sup> and [4+2]<sup>3</sup> as well as [2+2]<sup>4</sup> cycloadditions of singlet oxygen, and the catalytic<sup>5</sup> and stoichiometric<sup>5a,6</sup> epoxidations display a high (d.r. > 85:15) *threo* diastereoselectivity with chiral allylic alcohols, which are conformationally aligned through 1,3-allylic strain for selective  $\pi$ -facial attack.

Other than the above-mentioned photooxygenation,<sup>2–4</sup> the hydroxy-directing property of chiral allylic alcohols has not been utilized in other photochemical reactions,<sup>7</sup> e.g., the synthetically attractive [2+2] photocycloaddition of aldehydes and ketones to olefins (Paternò–Büchi reaction).<sup>8</sup> Examples of regioselective<sup>9</sup> and substrate-based diastereoselective<sup>10</sup> Paternò–Büchi reactions are known; however, moderate hydroxy-assisted enhancement of

Scheme 1



regioselectivity appears only to have been reported<sup>11</sup> for the [2+2] cycloaddition of olefinic alcohols to  $\alpha,\beta$ -unsaturated ketones (de Mayo reaction<sup>12</sup>). Moreover, since singlet oxygen is a rather special electronically excited species [low (only 23 kcal/mol) singlet energy for the <sup>1</sup> $\Delta_g$  state and high dipolar character] compared to the triplet-excited benzophenone [high (ca. 68 kcal/mol) triplet energy, pronounced diradical character], it was of mechanistic significance to assess whether the Paternò–Büchi photoreaction of benzophenone and chiral allylic alcohols is also subject to hydroxy-group directivity. Indeed, we report herein the highly regio- and *threo*-diastereoselective oxetane formation in the [2+2] photocycloaddition between benzophenone and chiral allylic alcohols **1** (Scheme 1). The allylic substrates **1** were chosen such that the oxetanes **2** possess a minimum of stereogenic centers to facilitate the configurational assignment of the cycloadducts.

The Paternò–Büchi reactions were performed on the semi-preparative scale at 10 °C in *d*<sub>6</sub>-benzene solution (0.25 M for each reactant). The samples were irradiated in a Rayonet photoreactor (350 nm) and subsequently analyzed by <sup>1</sup>H NMR spectroscopy directly on the crude photolyzate. The [2+2] photocycloaddition of benzophenone to the racemic allylic alcohols **1a–d** afforded only one regioisomer of the diastereomeric *threo*, *erythro*-**2a–d** oxetanes (Table 1, entries 1–5). For the hydroxy-protected silyl ether **1e**, however, the regioselectivity decreased significantly (83:17, which is equal to the inherent regioselectivity of 84:16 for the unfunctionalized 2-methyl-2-butene) and the reversed regioisomer **2e'** was also detected as mixture of diastereomers (Table 1, entry 6). In the nonpolar benzene, high to excellent ( $\geq 90:10$ ) diastereoselectivities were found for the substrates **1a–d** (Table 1, entries 1–4). The diastereomeric ratios exhibit a slightly increasing trend in favor of *threo* isomers with the steric demand of the R substituent (Me < Et < *i*-Pr); but for the large *tert*-butyl group, the *threo* diastereomer is formed exclusively (d.r.  $\geq 95:5$ , i.e., the *erythro* diastereomer was not detected in the <sup>1</sup>H NMR analysis). In contrast, the diastereoselectivity dropped drastically for the allylic alcohol **1a** in the presence of the protic methanol (Table 1, entry 5) and totally disappeared for the silyl ether **1e** (Table 1, entry 6).

The relative configuration of the major diastereomer (*threo*) was elucidated exemplarily for the *threo*-**2a** oxetane by means of X-ray analysis<sup>13</sup> (cf. Supporting Information) of the *threo*-**4a** ester, prepared by esterification with *p*-nitrobenzoyl chloride. The relative configurations of the remaining oxetanes **2b–d** were assigned by comparison of the <sup>1</sup>H NMR data with that of the *threo*-**2a** oxetane (cf. Supporting Information).

The very high regio- and diastereoselectivities in the oxetane formation in the nonprotic C<sub>6</sub>D<sub>6</sub> (entry 1), which are reduced in the presence of methanol (entry 5) and by protection of the OH

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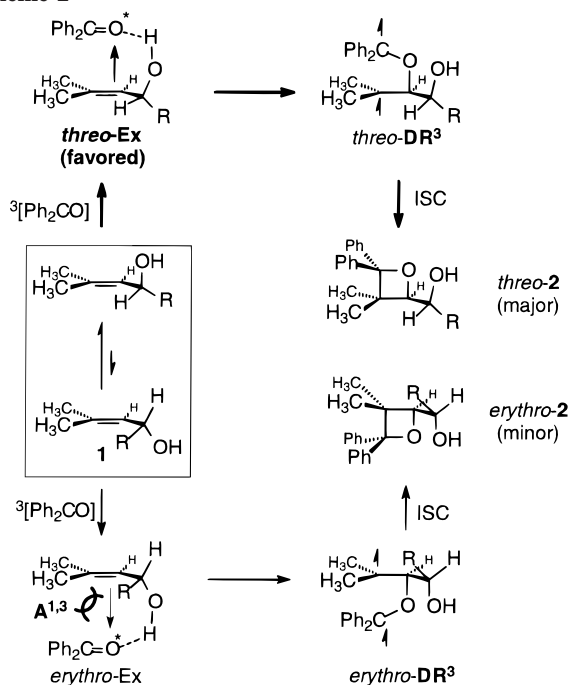
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**Table 1.** Photocycloadditions of Benzophenone to the Allylic Substrates **1a–e**

entry	substrate	X	R	solvent	time [h]	convn <sup>a</sup> [%]	m.b. <sup>a,b</sup> [%]	selectivities <sup>a</sup>	
								diastereo (threo:erythro)	regio (2:2')
1	<b>1a</b>	H	Me	C <sub>6</sub> D <sub>6</sub>	28	90	82	90:10	>95:05 <sup>c</sup>
2	<b>1b</b>	H	Et	C <sub>6</sub> D <sub>6</sub>	20	90	95	93:07	>95:05 <sup>c</sup>
3	<b>1c</b>	H	<sup>i</sup> Pr	C <sub>6</sub> D <sub>6</sub>	20	89	91	95:05	>95:05 <sup>c</sup>
4	<b>1d</b>	H	<sup>t</sup> Bu	C <sub>6</sub> D <sub>6</sub>	20	92	88	>95:05	>95:05 <sup>c</sup>
5	<b>1a</b>	H	Me	C <sub>6</sub> D <sub>6</sub> /D <sub>3</sub> COD (1:1)	32	85	81	69:31	95:05 <sup>c</sup>
6	<b>1e</b>	SiMe <sub>2</sub> Bu	Me	C <sub>6</sub> D <sub>6</sub>	32	84	85	52:48	83:17 <sup>c</sup>

<sup>a</sup> Determined by <sup>1</sup>H NMR spectroscopy directly on the crude product mixture. Error limits  $\pm 5\%$  of the given values. Internal standards: aromatic signals (entries 1, 5, 6), dimethyl isophthalate (entries 2–4). <sup>b</sup> Mass balance based on the allylic substrate **1**. <sup>c</sup> The diastereomeric ratio of the minor regioisomer **2'** is 78:22; the relative configurations have not been determined.

**Scheme 2**

group through silylation (entry 6), unequivocally establish the hitherto unprecedented hydroxy-directing effect in the Paternò–Büchi reaction; unquestionably, these excellent selectivities enhance the utility of this already synthetically valuable method. Due to 1,3-allylic strain ( $A^{1,3}$ ) between the R substituent and the *cis*-methyl group, the allylic alcohol is expected to be conformationally aligned such that the regioselective threo attack (Scheme 2, top) of the electronically triplet-excited benzophenone is favored through hydrogen bonding in the exciplex<sup>14</sup> (direct electron transfer to afford a radical-ion pair is unlikely for such a combination of Paternò–Büchi partners<sup>15</sup>). Subsequently, the favored threo exciplex transforms chemically to the triplet preoxetane diradical *threo-DR*<sup>3</sup>, which finally cyclizes to the *threo-2* oxetane as essentially exclusive photoproduct.

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Hydrogen bonding between the allylic alcohol and the incoming triplet-excited ketone as an attractive interaction accounts for the marked regio- and diastereoselectivity. Since this hydrogen bonding is reduced in the presence of the protic methanol (competitive intermolecular hydrogen bonding) and since the silyl ether **1e** cannot serve as hydrogen-bonding donor, the diastereoselectivity expectedly decreases (entries 5 and 6). As for the surprisingly high regioselectivity observed in the benzene/methanol mixture [only traces (ca. 5%) of **2a'** were detected (entry 5)], evidently, competitive hydrogen bonding by methanol is ineffective in influencing the regioselectivity by such external medium effects. In contrast, when the hydroxy group is masked by silylation (entry 6), a substantial decrease in the regioselectivity is obtained and also the reverse regioisomer **2e'** is observed. Therewith the general scope and applicability of the concept of hydroxy-group directivity<sup>1</sup> has been significantly extended: Besides the already established numerous ground-state epoxidations (catalytic, stoichiometric, homogeneous, heterogeneous, peroxidic, and organometallic oxidants), it encompasses now also photochemical reactions, namely the present triplet-state Paternò–Büchi cycloaddition and the previous singlet-state photooxygenations.<sup>4</sup>

In summary, these results establish that the regioselective and threo-diastereoselective [2+2] photocycloaddition of benzophenone to chiral allylic alcohols is hydroxy directed. Hydrogen bonding promotes the regioselectivity and, in combination with 1,3-allylic strain, excellent  $\pi$ -facial differentiation (high threo diastereoselectivity) is achieved. This advance in the control of selectivity opens up new perspectives for the already preparatively valuable Paternò–Büchi reaction in the diastereo- and regioselective synthesis of side-chain-functionalized oxetanes as building blocks.

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**Supporting Information Available:** Experimental details (PDF). This material is available in the Internet under <http://pubs.acs.org>.

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