

Paternò–Büchi Reactions of Allylic Alcohols and Acetates with Aldehydes: Hydrogen-Bond Interaction in the Excited Singlet and Triplet States?

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The concept of hydrogen-bonding as a tool for directing photochemical reactions has been reported for intermolecular [2 + 2] and [4 + 4]-cycloadditions.¹ The first example of such a Paternò–Büchi reaction (carbonyl-ene-photocycloaddition) with excellent diastereoselectivity control was described recently by Adam and co-workers.² In this reaction, a chiral allylic alcohol interacts with the first excited triplet state of benzophenone. Direction and magnitude of stereocontrol resembled the corresponding singlet oxygen ene reactions with the same substrates.³ At first glance, the first excited state of molecular oxygen and an electronically excited $n\pi^*$ state (singlet as well as triplet) of a carbonyl compound behave similar in their reactivity, that is, both are electrophilic species and prefer similar interaction paths with unsaturated substrates. With respect to the state-of-the-art mechanistic concepts, however, both reactions strongly differ, and the parallelism in stereocontrol is striking. For the singlet oxygen ene reaction, a perepoxide mechanism is favored,⁴ Paternò–Büchi reactions with singlet excited carbonyls proceed via conical intersections,⁵ triplet carbonyl-ene reactions pass through triplet 1,4-biradical intermediates.⁶ Prior to these intermediates, exciplexes have been postulated which might also be sensitive toward hydrogen bonding interaction.⁷ On the other hand, it was shown that the $n\pi^*$ excitation of carbonyls in the presence of protic solvents is blue-shifted,⁸ that is hydrogen bonding increases the excitation energy, a well-known fact in Norrish chemistry.⁹ An appropriate mechanistic concept which explains the extent and direction of stereocontrol is still lacking. Thus, we addressed the following questions: (a) is there a specific spin-directing effect connected with hydrogen-bonding, (b) do hydrogen-bonding interactions influence induced as well as noninduced (“simple”) diastereoselectivity of the Paternò–Büchi reaction, (c) does hydrogen-bonding effect the rate of the Paternò–Büchi reaction?

The role of hydrogen-bonding interactions in the Paternò–Büchi reaction (PBR) of allylic alcohols can be easily tested by comparison of the free alcohols with the O-protected substrates, for example, the corresponding acetates. As a typical triplet precursor, benzaldehyde was irradiated in the presence of prenol (**1**) and prenyl acetate (**2**), respectively. Additionally, three aliphatic aldehydes which can react either from their singlet as

Scheme 1. PBR of Prenol and Prenyl Acetate

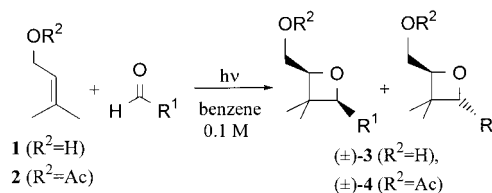


Table 1. PBR of Prenol and Prenyl Acetate

R ¹ =	cis/trans-3	cis/trans-4
Me (a)	81:19	77:23
Et (b)	86:14	81:19
^t Bu (c)	83:17	80:20
Ph (d)	>97:3	93:7

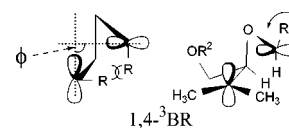


Figure 1. Simple diastereoselectivity: triplet biradical geometries.

well as triplet excited states were applied (all 0.1 M in benzene). From all substrate combinations, the *cis*-oxetanes were formed as the major diastereoisomers in moderate to good yields. The relative configurations of the major diastereoisomers were unambiguously determined from the NOE effects which were detected for one of the *gem*-methyl groups by saturation of both methine H and by NOE between the methylene H of the two side chains. The d.r. values were nearly identical for the three aliphatic aldehydes in the reaction with prenol but slightly higher than with prenyl acetate. Benzaldehyde gave exclusively (>97:3) the *cis*-diastereoisomer **3d** from **1**, with prenyl acetate a 93:7 mixture of **4d** was isolated (Scheme 1).

Conclusion I. The regioselectivity of the PBR with **1** and **2** is high (ca. 20% regioisomeric oxetanes for benzaldehyde addition, <5% from aliphatic aldehydes) and corresponds to the classical biradical stabilization concept.^{7,10b} This comparison showed that hydrogen-bonding is not responsible for controlling product regiochemistry, at least not in these cases. The simple diastereoselectivity is moderate with aliphatic aldehydes and high for benzaldehyde. Comparing prenol with its acetate shows, that hydrogen bonding might slightly increase the *cis/trans*-selectivity, but also other reasons such as steric effects can explain the marginal differences. From the numbers in Table 1, one can unambiguously derive that the triplet excited carbonyl state reacts highly *cis*-selective with prenol (to give **3d**) and prenyl acetate (to give **4d**). This selectivity can be rationalized by the assumption of spin-orbit coupling (SOC)-controlled intersystem crossing (ISC) geometries at the stage of the triplet 1,4-biradical.¹⁰

Optimal ϕ -values for strong SOC are expected in the 90 ± 10° range.¹¹ This model presupposes conformational flexibility (and mobility) at this intermediate triplet stage in contrast to the corresponding singlet reactions where conical intersections guide the substrate to the products nearly barrier-free.⁵ A view along the C3–C4 bond (Figure 1) of the intermediate 1,4-³BR shows the relevant contribution to the high degree of stereoselectivity: increasing *gauche* interactions were expected for biradical approach from the same *half space* as the hydroxymethyl or

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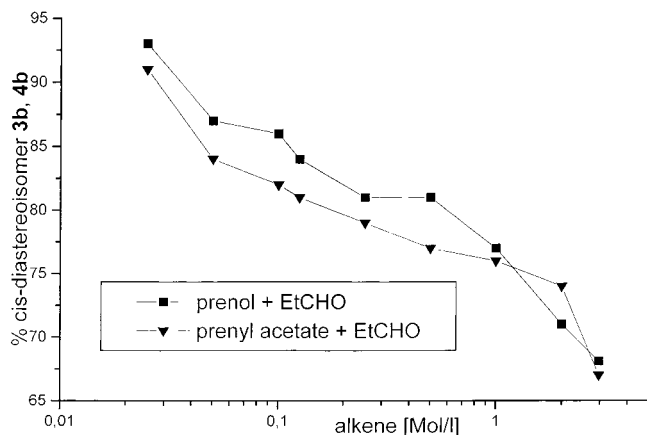


Figure 2. Concentration dependence of propionaldehyde PBR with **1** and **2**.

acetoxymethyl group, respectively. An additional internal hydrogen bond between the hydroxy group ($R^2 = H$) and the oxygen atom at position 2 of the 1,4-³BR slightly increases this conformational preference.¹²

To evaluate the differences in simple diastereoselectivity of the PBR in the triplet versus the singlet channel, we investigated the concentration dependence of the reaction of propionaldehyde with **1** and **2**. As already described for analogous reactions with 2,3-dihydrofuran as alkene component,¹³ the spin profile of a bimolecular photochemical reaction can be mapped by variation of substrate concentration, provided that the lifetime of the excited singlet state allows diffusion-controlled processes. This is the case for aliphatic aldehydes which have lifetimes in the 1–2 ns range.¹⁴ The results are shown in Figure 2.

At higher alkene concentration (alkene and aldehyde were used in equimolar concentrations) the simple *cis/trans*-stereoselectivity is identical (ca. 2:1) with both substrates **1** and **2**. In the low concentration region, the selectivity increases constantly to values >9:1 always with the prenyl reactions being slightly more selective.

Conclusion II. The curvature of the spin map indicated, that very high selectivities are expected for “pure” triplet reactions, whereas the singlet excited carbonyls only give moderate (if any) selectivity. This perfectly corresponds to our recent results on the spin-directed PBR with cyclic alkenes and clearly shows that the SOC-determined ISC-geometry model is a powerful rationale for explaining simple diastereoselectivities originating from 1, *n*-triplet biradical combinations.¹²

Further competition experiments were performed to examine the difference in reactivity comparing free and O-protected allylic alcohols. As standard olefin, we used 2,3-dihydrofuran in equimolar concentrations (Scheme 2). First, benzaldehyde was applied as triplet state precursor (entry A, Table 2).

From the ratio of prenyl-cycloadduct **3d** and the dihydrofuran-product **5**, it was concluded that these alkenes have similar reactivities with triplet $n\pi^*$ carbonyls. The results with propionaldehyde corroborated this result for the singlet (high concentrated region, entry B) and the triplet (low concentrated region, entry C) $n\pi^*$ state of an aliphatic aldehyde. Prenyl acetate (**2**) gave the adduct **4b** in minor quantities and the dihydrofuran adduct **5** prevailed. Thus, the reactivity difference between prenyl and

Scheme 2. Competition Experiments

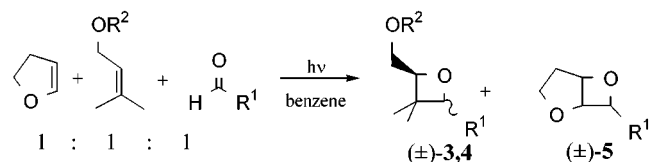
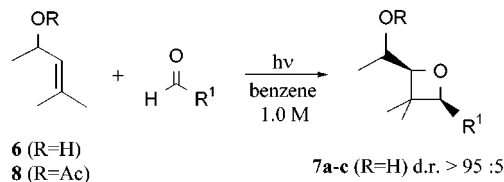


Table 2. Results of Competition Experiment

entry	R ¹ =	R ² =	concentration, M	3,4:5
A	Ph	H	1.0	47:53
B	Et	H	1.0	55:45
C	Et	H	0.01	60:40
D	Et	Ac	1.0	13:87

Scheme 3. PBR of RCHO with Chiral Allylic Alcohol/Acetate **6** and **8**



prenyl acetate is approximately 3¹⁵ which can originate either from hydrogen-bonding activation or simply from electronic deactivation of the alkene.

As recently published, chiral allylic alcohols react with triplet excited benzophenone with high *threo*-selectivity.³ This behavior was also observed for other triplet excited aromatic carbonyl compounds.¹⁶ Aliphatic aldehydes, which showed moderate *cis/trans*-selectivity with prenyl, gave high simple and induced diastereoselectivity, for example propionaldehyde added to **6** to give only one diastereoisomer **7b** in >95% selectivity.

When the corresponding allylic acetate **8** was reacted with aliphatic aldehydes, a mixture of all four diastereoisomers resulted, and the *threo/erythro*-selectivity for the *cis*-isomers dropped (Scheme 3).¹⁷

Conclusion III. In light of the mechanistic picture shown in Figure 1, an increase in bulk of the hydroxyalkyl sidechain is expected to lead to an increase in simple diastereoselectivity due to increasing steric interactions in one half-space of the ISC-reactive conformer. This effect was also apparent for the corresponding allylic acetate and thus is not coupled with hydrogen-bonding interactions and also vanishes in the singlet manifold (Figure 2). When allylic 1,3-strain operates (as in substrates **6** and **8**), an additional selectivity increase is observed which is connected with hydrogen-bonding interaction with singlet as well as triplet excited carbonyl states prior to bond formation. Thus, a hydroxy group directing effect can be postulated for the interaction of electronically excited $n\pi^*$ states with appropriate allylic substrates which accounts for the build-up of charge-transfer character during the approach of the reactants.^{10b}

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Supporting Information Available: Details of the photocycloaddition reactions, synthesis of starting materials, NMR-spectroscopic data of the oxetanes **3a–3d**, **4a–4d**, and *threo*-**7a–7c** as well as the oxetanes from **8**; NOE spectra of **3b** (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(17) From **8** and acetaldehyde a 56:25:12:7 diastereoisomeric mixture was isolated.

(12) One of the reviewers informed us that the energy difference (B3LYP/6-31G*) between the two diastereoisomeric 1,4-triplet biradicals from formaldehyde and **6** is near to zero. This is in account with our assumption that the asymmetric induction (Scheme 3) in chiral allylic alcohols originates from hydrogen-bonding interactions (prior to ring formation), whereas the simple diastereoselectivity (Scheme 1) originates from ISC-reactive conformers (Figure 1).

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