Temperature and Viscosity Dependence of the Spin-Directed Stereoselectivity of the Carbonyl–Alkene Photocycloaddition**

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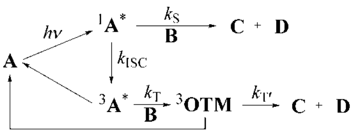
The unusual nonlinear temperature dependence of the stereoselectivity of Paternò–Büchi photocycloadditions of electron-rich cycloalkenes with chiral phenyl glyoxylates served as the basis for the development of the isoinversion principle by Scharf and co-workers.[1] The influence of the excited-state spin multiplicity was not observed in these studies as substrates with high intersystem crossing (ISC) rates were used and thus exclusive (bimolecular) triplet reactions were expected.[2] However, the ISC-process from the triplet 1,4-biradical (2-oxatetramethylene),[3] which is necessary to form the closed-shell product, was not discussed as a further possible selection step in the context of the isoinversion principle.

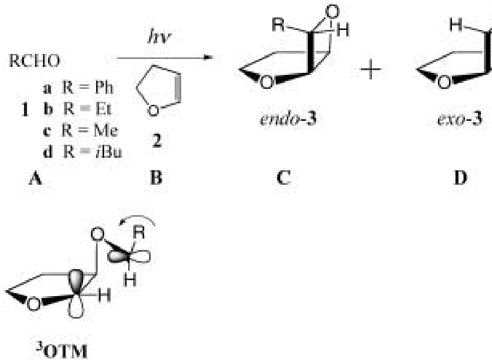
Inversion effects in stereoselectivity/temperature correlations were observed also for other photochemical[4] as well as for a multitude of thermal processes.[5] Despite several attempts to understand these effects theoretically,[1] their origin is still debatable.[6] A simplified model interprets the inversion points in the selectivity/temperature correlation as changes between two selection stages that are controlled to a different by the respective differences in activation enthalpy and entropy degree.[1] Alternatively inversion regions can be postulated which result from a change in the rate-determining step.[7]

In recent years we have analyzed closely the mechanism of the terminal bond-forming step in triplet [2+2] photocycloadditions with an emphasis on the non-induced ("simple") diastereoselectivity.[8] The detection of the concentration dependence of the stereoselectivity of the Paternò–Büchi reaction was essential for demonstrating different simple diastereoselectivities in singlet and triplet routes.[9] Each pair of carbonyl and alkene components exhibited a characteristic substrate concentration at which point a 1:1 ratio of singlet and triplet reactivity, that is, spin selectivity, could be detected. The shape of these concentration/diastereoselectivity correlations reflects the different kinetic contributions to this complex reaction scenario (Scheme 1). The C/D selectivity is controlled by the geometry of the conical intersection in the case of the singlet reaction (k_S)[10] and by the optimal ISC geometry of the 2-oxatetramethylene biradical (^{3}OTM) in the case of the triplet reaction ($k_{T'}$).[11]



Scheme 1. Mechanism for a photocycloaddition that involves singlet and triplet states.

Our initial assumption was that the activation parameters should strongly differ for these two processes and consequently characteristic nonlinear behavior might occur during temperature variation. Prior to these experiments, solvent viscosity effects in triplet and singlet photocycloadditions were studied to separate these influences from temperature effects. The photocycloaddition of benzaldehyde (**1a**) with 2,3-dihydrofuran (**2**) was investigated as a typical triplet reaction with concentration-independent diastereoselectivity (Scheme 2).[9]



Scheme 2. Photocycloaddition of **2** with **1a–d**.

The variation of the solvent viscosity over a large range ($\eta = 0.3$ to 1500 cP)[12] resulted in a weak but significant increase in *endo* selectivity from 82% to 91% (Table 1, Figure 1).[13] More pronounced effects were detected in the analogous reactions with aliphatic aldehydes **1b–d** and dihydrofuran (1M substrate concentrations). In all cases, the diastereoselectivity increased with increasing solvent viscosity (the value for the reaction of **1b** in glycerol is omitted in Figure 1). In our mechanistic model (Scheme 1), an increase in solvent viscosity should favor the triplet channel as a result of a reduction in the diffusion rate limit (about 4 orders of magnitude in the viscosity range).[14] Thus the viscosity of the medium only slightly influences the diastereoselectivity of the triplet photocycloaddition ($k_{T'}$) which is controlled by the geometry of the 2-oxatetramethylene triplet 1,4-biradical (^{3}OTM).[8, 11] The influence of the solvent viscosity on the diastereoselectivity of the singlet reaction, which can be estimated from the correlation (Figure 1), is more distinct.

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Table 1. Viscosity dependence of the diastereoselectivity of the Paternò–Büchi reaction of **2** (1 M) with **1a** (1 M) and **1b** (1 M) at 293 K.

Solvent	η [P]	k_{diff}[a]	k'_{Diff}[b]	*endo*/*exo*[c] for **2**+**1a**	*endo*/*exo* for **2**+**1b**[d]
n-hexane	0.0033	1.8×10^{10}	2.9×10^{10}	82:18	45.3:54.7
acetonitrile	0.0036	1.6×10^{10}	2.6×10^{10}	82:18	45.3:54.7
n-heptane	0.0041	1.4×10^{10}	2.3×10^{10}	85:15	48.6:51.4
methanol	0.0060	9.8×10^{9}	1.6×10^{10}	84:16	49.6:50.4
ethanol	0.012	4.8×10^{9}	7.9×10^{9}	86:14	50.4:49.6
n-propanol	0.023	2.5×10^{9}	4.1×10^{9}	90:10	52.1:47.9
n-butanol	0.029	2.0×10^{9}	3.3×10^{9}	87:13	53.6:46.4
n-octanol	0.085	6.9×10^{8}	1.1×10^{9}	89:11	57.5:42.5
glycol	0.20	2.9×10^{8}	4.7×10^{8}	83:17	59.0:41.0
1,2-propanediol	0.56	1.0×10^{8}	1.6×10^{8}	87:13	60.5:39.5
1,4-butanediol	0.89	6.6×10^{7}	1.1×10^{8}	91:9	72.6:27.4
glycerol	15.0	3.9×10^{6}	6.3×10^{6}	[e]	80.2:19.8

[a] $k_{\text{diff}} = 2 \times 10^5 T/\eta$. [b] $k'_{\text{Diff}} = 8 \times RT/2000$ (ref. [12]). [c] Determined by means of NMR spectroscopic analysis of the crude product mixture (±2%). [d] Determined by means of GC analysis of the crude product mixture (±1%). [e] Could not be determined.

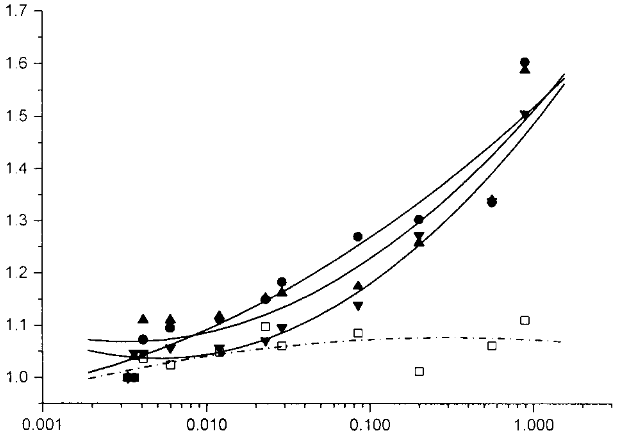

Figure 1. Viscosity dependence of the diastereoselectivity of the Paternò–Büchi reaction of **2** with **1a–d** (**1a**: □; **1b**: ●; **1c**: ▲; **1d**: ▼) at 293 K; y = *endo*/*exo*-diastereoselectivity (normalized to 1.0 for the lowest solvent viscosity).

The temperature dependence of the Paternò–Büchi reaction was subsequently studied in the triplet reaction between **1a** and **2**. No influence was detected, within an error margin. The concentration dependence of the Paternò–Büchi reaction at different temperatures was investigated with the standard system propionaldehyde (**1b**) and **2** in *n*-hexane (Figure 2). This substrate combination was used primarily to determine the different simple diastereoselectivities of singlet and triplet photocycloadditions.[9]

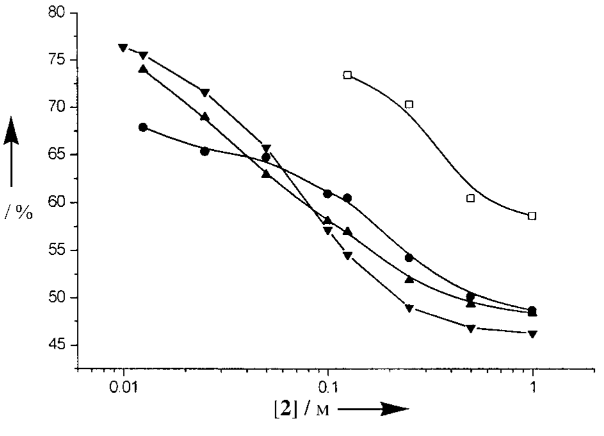

Figure 2. Concentration dependence of the Paternò–Büchi reaction of **2** with **1b** at different temperatures (+25 °C: ●; +10 °C: ▲; −14 °C: ▼; −78 °C: □) in *n*-hexane; y = *endo*-selectivity.

In the temperature region between −14 and +25 °C, the diastereoselectivity/concentration correlation showed only small changes, whereas at lower (−78 °C) temperatures the point of isospinselectivity is shifted significantly to higher concentrations. This shift is not proof for nonlinear temperature dependence, but a clear indication that not only the concentration, but also the temperature influences the diastereoselectivity of photocycloadditions with carbonyl compounds, which can react in their S_1 and T_1 states. In a next series of experiments, the temperature dependence of the *endo*/*exo*-selectivity was investigated at constant concentration (1 M). The aliphatic aldehydes **1b–d** gave characteristic nonlinear curves with inversion points for **1c** and **1d** (Figure 3).

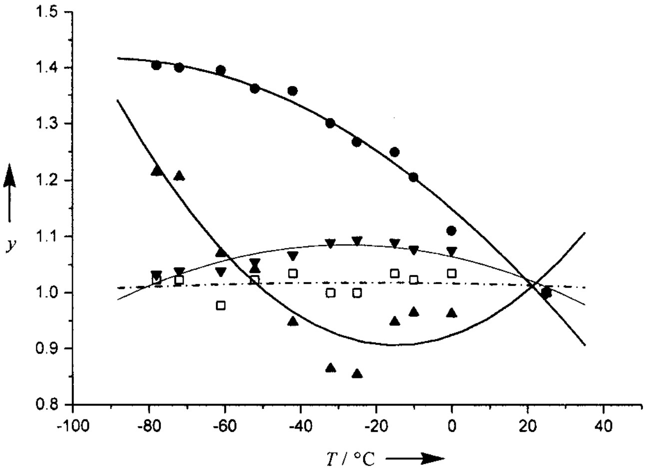

Figure 3. Temperature dependence of the Paternò–Büchi reaction of **2** with **1a–d** (**1a**: □; **1b**: ●; **1c**: ▲; **1d**: ▼) in *n*-hexane; y = *endo*/*exo*-diastereoselectivity (normalized to 1.0 for 23 °C).

The **1c**/**2** system shows the strongest deviation from linearity with an inversion temperature of −37 °C. For this specific reaction, we have learned from concentration studies that the acetaldehyde triplet adds to 2,3-dihydrofuran with high *endo* selectivity (up to 85%), whereas the singlet gives the same products with moderate *exo* selectivity (up to

65 %).[9] Thus, the temperature correlation can be interpreted qualitatively as follows: at room temperature under high concentration conditions, the cycloadducts **3c** were formed with low *exo* selectivity, predominantly through the singlet channel. This selectivity increases with decreasing temperature (as intuitively expected) and reaches an inversion point at −17 °C (Figure 3). At this point, the triplet reactivity gains sufficient influence to increase the *endo* selectivity. The rate of the intersystem-crossing process (k_{ISC}) is expected to be nearly temperature independent.[15]

This selectivity reversal could be detected for the **1c**/**2** system in a temperature region that is experimentally accessible. A marginal change in activation parameter, however, catapults this effect out of the experimental window (+40 to −78 °C). This might have been the reason why we did not see an inversion effect in the propionaldehyde photocycloaddition. If this assumption is true, a change in substrate concentration might shift the inversion region back into the experimentally accessible range. Thus, we measured the temperature dependence of the **1b**/**2** system at 5 M (both substrates) and indeed detected an inversion point at −27 °C. Presumably, in this case an increase in concentration led to a low-temperature shift of the inversion region (Figure 4). The reverse should be observed in reactions with their inversion points at low temperatures; which could be shifted to higher temperature with concentration variation. Yet, this effect could not be verified experimentally.

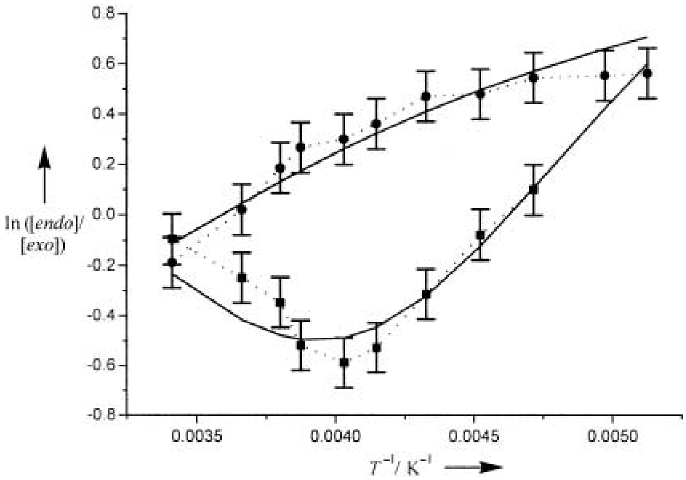

Figure 4. Plots of ln ([*endo*]/[*exo*]) versus 1/*T* for the Paternò–Büchi reaction of **2** with **1b** at concentrations of 1 M (●)and 5 M (■) in *n*-hexane.

To determine the kinetic parameters we simulated the curves shown in Figure 4. The simulations were carried out based on the following considerations: the amount of product P_j formed, which in the present case is either the *exo* or *endo* oxetane **3** from the singlet and triplet channels, is given by Equation 1 (with four channels: *exo* ($j=1$) and *endo* ($j=2$) from the singlet state, as well as *exo* ($j=3$) and *endo* ($j=4$) from the triplet state of the aldehyde).

$$P_j = A_j e^{\frac{-E_j}{RT}} \tag{1}$$

Because the lifetime of the S_1 state of aliphatic aldehydes is of the order of ~1 ns,[16] the reaction probability from the singlet channel is further restricted by molecular diffusion. Under such conditions, the photophysical deactivation processes compete with the photochemical channels. Thus in dilute solutions the probability of reaction from the singlet channel (R_S) decreases and the probability of triplet population (ϕ_T) increases. On the other hand, when the concentrations of the aldehyde and olefin are increased, though one expects reaction from the singlet channels to dominate, other processes such as collisional quenching of the excited singlet and triplet aldehyde by the ground-state aldehyde cannot be ignored. If the temperature is lowered, a diffusion-controlled decrease in the reaction from the singlet channel is expected. As a result of the ≈200-fold longer lifetime of the T_1 state of the aldehyde (200–400 ns)[16] the reaction probability (R_T) from the triplet channel should be less dependent on the temperature.[17] From our previous studies we know that at concentrations above 1 M, the reaction of **1b** and **2** takes place only through the singlet channel at room temperature.[18] Normalized temperature-dependent reaction probabilities from the singlet and triplet channels with respect to room temperature (300 K) can be approximated by Equations 2a and b. The exponent *n* reflects the nonlinearity of the temperature-dependent contributions from molecular diffusion, viscosity, and concentration.[19]

$$R_S = (T/300\,\mathrm{K})^n \tag{2a}$$

$$R_T = (1-R_S)\phi_T \tag{2b}$$

From the concentration studies at 300 K, we know the *endo*/*exo* ratios for pure singlet and triplet channels.[9] By using this information we can reduce the number of parameters according to Equations 3 and 4.

$$S^{300\mathrm{K}}_{endo/exo} = \frac{P_2}{P_1} = \frac{A_2}{A_1} e^{\frac{-(E_2-E_1)}{300\mathrm{K}\,R}} \tag{3}$$

$$E_1 = E_2 + 300\mathrm{K}\,R \ln\left(\frac{S^{300\,\mathrm{K}}_{endo/exo} A_1}{A_2}\right) \tag{4}$$

For the triplet channel, the corresponding Equation 5 is used.

$$E_3 = E_4 + 300\,\mathrm{K}\,R \ln\left(\frac{S^{300\,\mathrm{K}}_{endo/exo} A_3}{A_4}\right) \tag{5}$$

Thus, the temperature-dependent overall *endo*/*exo* ratio Σ is given by Equation 6.

$$\Sigma^T_{endo/exo} = \frac{R_S P_2 + (1-R_S)\phi_T P_4}{R_S P_1 + (1-R_S)\phi_T P_3} \tag{6}$$

The *endo*/*exo* selectivity was simulated with the use of these eight parameters for 1-M and 5-M concentrations of the aldehyde and dihydrofuran (Figure 4).

The reliability of the present simulations (notwithstanding the large number of parameters) comes from the fact that after fitting the experimental data from 5-M solutions, all the other parameters were fixed, and only *n* and ϕ_T were varied to simulate the curve for the 1-M data. It should be noted that these variable parameters are not independent, but are highly correlated with each other.[20] The "selectivity inversion" can be interpreted qualitatively: the activation barrier for the formation of the *exo* product (E_1) from the singlet channel is much smaller than for the formation of the *endo* product. However, the pre-exponential factor for the *endo* product is larger than for the *exo* product. With decreasing temperature, the exponential part dominates and more *exo* than *endo* product is formed.

The situation is completely different for triplet channel: the formation of both the *endo* and *exo* products has almost no barrier, whereas the pre-exponential factors favor the formation of the *endo* product. As a result of the lack of activation barrier for both the products, the *endo*/*exo* ratio from the triplet channel should not be temperature dependent. This has been proved experimentally in the case of the photocycloaddition of **1a** with **2** (see Supporting Information). If the reaction probabilities R_S and R_T were not temperature dependent, then no "selectivity inversion" would be observed. The temperature-dependent reaction probabilities R_S and R_T are reflected in the values n and ϕ_T. At the higher concentration (5 M), n is large, thus reflecting a faster decrease in the reaction probability (R_S) from the singlet channel. This may be caused by quenching of the excited singlet aldehyde molecule by the ground-state aldehydes. Similarly, the relative triplet quantum yield (ϕ_T) is very small, which implies that at higher concentrations the majority of the excited singlet aldehyde molecules react or are deactivated. At the lower concentration (1 M), n is small and R_S decreases less steeply with temperature and $(1 - R_S)$ increases correspondingly from the initial value of 0 at 300 K. Simultaneously, the relative triplet population ϕ_T is predicted to be close to 1.0. Thus, both singlet and triplet channels compete with each other at 1 M concentration. With decreasing temperature, the triplet contribution increases. As a result of the larger *endo*/*exo* selectivity from the triplet channels (5.6)[9] with decreasing temperature, the total *endo*/*exo* ratio increases steadily.

The simulations do not indicate an abrupt change in the selectivity correlation as is the case in isoinversion curves,[1] but an inversion region as described by Hale and Ridd.[7] From our model we expect this inversion region to lie outside the experimental window for many substrate combinations, either in photochemical or thermal reactions. Thus, inversion phenomena might often be overlooked. Variations of the substrate concentrations, however, change the inversion region strongly and represent an additional method of shifting the "inversion point" into the experimental region.

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[1] H. Buschmann, H.-D. Scharf, N. Hoffmann, M. W. Plath, J. Runsink, *J. Am. Chem. Soc.* **1989**, *111*, 5367–5373.

[2] A contrasting behavior was described for aromatic acyl cyanides: C. Zagar, H. D. Scharf, *Chem. Ber.* **1991**, *124*, 967–969.

[3] a) S. C. Freilich, K. S. Peters, *J. Am. Chem. Soc.* **1981**, *103*, 6255–6257; b) R. A. Caldwell, T. Majima, C. Pac, *J. Am. Chem. Soc.* **1982**, *104*, 629–630; c) S. C. Freilich, K. S. Peters, *J. Am. Chem. Soc.* **1985**, *107*, 3819–3822. Concerning the customary terminology, the ISI Citation Database lists (1993 to 2001) 1240 references for "biradical" and 886 references for "diradical".

[4] a) N. Braussand, N. Hoffmann, H.-D. Scharf, *Tetrahedron* **1997**, *53*, 14701–14712; b) J. Muzart, F. Hénin, J.-P. Pète, A. M'Boungou-M'Passi, *Tetrahedron: Asymmetry* **1993**, *4*, 2531–2534; c) J. Muzart, F. Hénin, S. J. Aboulhoda, *Tetrahedron: Asymmetry* **1997**, *8*, 381–389; d) T. Bach, K. Jödicke, *Chem. Ber.* **1993**, *126*, 2457–2466; e) D. Becker, Y. Cohen-Arazi, *J. Am. Chem. Soc.* **1996**, *118*, 8278–8284.

[5] a) H. Buschmann, H.-D. Scharf, N. Hoffmann, P. Esser, *Angew. Chem.* **1991**, *103*, 480–518; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 477; b) D. Heller, H. Buschmann, H.-D. Scharf, *Angew. Chem.* **1996**, *108*, 1964–1967; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1852–1854; c) A. Wiegers, H.-D. Scharf, *Tetrahedron: Asymmetry* **1996**, *7*, 2303–2312; d) M. A. MeyerStork, D. Haag, H.-D. Scharf, *J. Chem. Soc. Perkin Trans. 2* **1997**, 593–595; e) T. Göbel, K. B. Sharpless, *Angew. Chem.* **1993**, *105*, 1417–1418; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1329–1331; f) G. Cainelli, D. Giacomini, P. Galletti, *Chem. Commun.* **1999**, 567–572.

[6] L. Liu, Q.-X. Guo, *Chem. Rev.* **2001**, *101*, 673–695.

[7] K. J. Hale, J. H. Ridd, *J. Chem. Soc. Chem. Commun.* **1995**, 357–358.

[8] A. G. Griesbeck, H. Mauder, S. Stadtmüller, *Acc. Chem. Res.* **1994**, *27*, 70–76.

[9] A. G. Griesbeck, M. Fiege, S. Bondock, M. S. Gudipati, *Org. Lett.* **2000**, *2*, 3623–3625.

[10] I. J. Palmer, I. N. Ragazos, F. Bernardi, M. Olivucci, M. A. Robb, *J. Am. Chem. Soc.* **1994**, *116*, 2121–2132.

[11] A. Kutateladze, *J. Am. Chem. Soc.* **2001**, *123*, 9279–9282.

[12] The η-values were taken from a publication on the photodenitrogenation of azoalkanes: W. Adam, V. Marti, C. Sahin, A. V. Trofimov, *J. Am. Chem. Soc.* **2000**, *122*, 5002–5003.

[13] Changes in solvent polarity do not influence the simple diastereoselectivity; however, they strongly change the regioselectivity of the Paternò–Büchi reaction: A. G. Griesbeck, S. Buhr, M. Fiege, H. Schmickler, J. Lex, *J. Org. Chem.* **1998**, *63*, 3847–3854.

[14] This is obtained by using the Debye equation: $k_{\text{diff}} = 2 \times 10^5 \, T/\eta$: P. Debye, *Trans. Electrochem. Soc.* **1942**, *82*, 265; or alternatively by using the modified equation: $\mathrm{k}'_{\text{Diff.}} = 8 \times RT/2000\eta$. See also: P. J. Wagner, I. Kochevar, *J. Am. Chem. Soc.* **1968**, *90*, 2232–2238.

[15] For ISC of azoalkanes, see: M. H. Chang, D. A. Dougherty, *J. Am. Chem. Soc.* **1982**, *104*, 2333–2334; N. J. Turro, C. A. Renner, W. H. Waddell, T. J. Katz, *J. Am. Chem. Soc.* **1976**, *98*, 4320–4322; for ISC of aromatic hydrocarbons, see: J. B. Birks in *Organic Molecular Photophysics* (Ed.: J. B. Birks), Wiley, New York, **1973**, pp. 39–45.

[16] J. Kossanyi, S. Sabbah, P. Chaquin, J. C. Ronfart-Haret, *Tetrahedron* **1981**, *37*, 3307–3315.

[17] The quantum yield for the "pure" triplet reaction of **1a** with **2** was determined by means of valerophenone actinometry (benzene; extrapolation to 0% conversion): $\phi = 0.48$; see: P. J. Wagner, A. E. Kemppainen, *J. Am. Chem. Soc.* **1972**, *94*, 7495–7499; for applications to Paternò–Büchi reactions, see: M. Abe, E. Torii, M. Nojima, *J. Org. Chem.* **2000**, *65*, 3426–3431.

[18] The Stern–Volmer analysis of the fluorescence quenching of propionaldehyde by 2,3-dihydrofuran resulted in $k_q = 2.2 \times 10^9 \, \mathrm{M}^{-1} \mathrm{s}^{-1}$ with $\tau(S_1) = 1.8 \times 10^{-9}$ s.

[19] Attempts to express this dependence numerically led to less accurate results as a result of an increase in the number of unknown parameters.

[20] Parameters for simulation of the reaction of **2** with **1b**: $E_1 = 157$, $E_2 = 8992$, $E_3 = -12.5$, and $E_4 = 5.8 \, \mathrm{J\,mol^{-1}}$; $A_1 = 0.054$, $A_2 = 1.599$, $A_3 = 0.057$, $A_4 = 0.327$; at 5 M: $n = 8.99$, $\phi_T = 0.0079$; at 1 M: $n = 0.88$, $\phi_T = 0.9975$. Only relative values for the preexponential factors resulted from the simulation.

1433-7851/01/4024-4687 $ 17.50+.50/0