Spin-dependent diastereoselectivity in the photocycloaddition of aldehydes to 2,2-dimethyl-2,3-dihydrofuran

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ABSTRACT. The simple (non-induced) diastereoselectivity of the photocycloaddition of aliphatic as well as aromatic aldehydes to 2,2-dimethyl-2,3-dihydrofuran (**1**) was analyzed as a function of the substrate concentration (spin mapping) and rationalized in terms of optimal spin-orbit coupling controlled triplet biradical geometries.

1. INTRODUCTION

The technique of "spin-mapping" of diastereoselectivities of bimolecular photochemical reactions is of special relevance in reactions of electronically excited molecules and decisive in controlling and manipulating the stereochemistry of photocycloaddition reactions [1]. In a series of publications, we have recently described the effect of substrate concentration on the spin-selectivity [2] of the Paternò-Büchi reactions of aliphatic aldehydes with 2,3-dihydrofuran [3], allylic alcohols [4], and cyclooctene [5], as well as temperature and viscosity dependence of these reactions [6]. More recently, we have also investigated the ^{2}H magnetic isotope effect on the stereoselectivity in singlet and triplet photocycloaddition reactions [7]. Paternò-Büchi reactions with singlet excited carbonyls most probably proceed *via* conical intersections, the reactions between triplet excited carbonyls and alkenes pass through triplet 1,4-biradical intermediates [8]. Whereas benzaldehyde and derivatives are applied as reactive triplet species, naphthaldehydes can be used in Paternò-Büchi reactions as reactive singlet excited components [9]. The Paternò-Büchi reaction of β-naphthaldehyde with 2,3-dihydrofuran is a singlet process (as shown by—non productive-triplet sensitization experiments) and gave predominantely the thermodynamically favoured *exo*-diastereoisomer. Griesbeck and Mattay have reported that an increase in steric demand of the α-substituent at the carbonyl component improved the *endo/exo* ratio. Methyl trimethylpyruvate with the sterically more demanding *tert.*-butyl group gave solely the thermodynamically disfavoured *endo*-diastereoisomeric oxetane (d.s. > 98%) with a dioxolene substrate [10]. Similar results were obtained for 2,2-bis-isopropyl-1,3-dioxolene; in this case the *endo/exo*-ratio of the bicyclic oxetane product is inverted when going from the triplet excited mesitylaldehyde to the singlet excited naphthaldehyde as substrate. Two structural features made the conformational analysis of spin-inversion geometries straightforward: the two sites of the alkene part were strongly differentiated concerning the degree of substitution and steric hindrance. The alkenes investigated in these studies were always cyclic, thus reducing the conformational flexibility at the biradical stage. The situation became more complex when one or both of these structure features is modified. Methyl-substituted cycloalkenes have two ISC-reactive sites and thus, the *endo/exo*-ratios dropped significantly [11]. An extreme example was 1,2-dimethylcyclobutene: the Paternò-Büchi reaction of this substrate with benzaldehyde resulted solely in the *exo*-diastereomer. This is exactly predicted by the "ISC-geometry model" [12] which is depicted in Figure 1 and relates to an orthogonal approach of the radical centers in a triplet 1,4-biradical because of an optimized spin-orbit coupling (SOC) value [13].

In case of the bis-methylated cycloalkene, one side is now sterically more demanding (compared to unsubstituted starting materials) and the biradical combination trajectory involves the approach from the less shielded cyclobutene plane. Steric hindrance can also reach a critical value during bond formation and might favor the formation of the thermodynamically more stable product. Park and coworkers [14] described the photocycloaddition of benzaldehyde to 2,2-diethoxy-3,4-dihydro-2H-pyran which gave preferentially the *exo*-phenyl product (d.e. 92%).

In order to expand our recent studies on the spin-mapping of *endo/exo*-diastereoselectivities, we envisaged to modify the cycloalkene part in such a way that the thermodynamic preference of the *exo*-diastereoisomer is strongly enhanced. From such an approach we expected a more distinct effect on the

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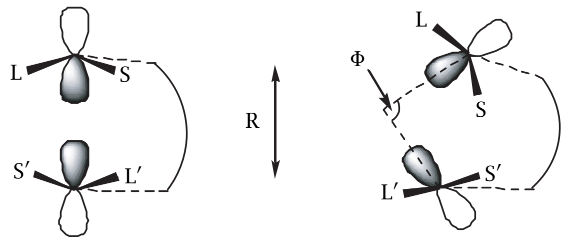
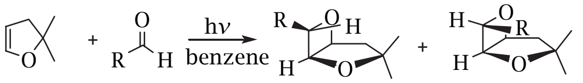


Figure 1. *The “ISC-geometry model”: optimal spin-orbit coupling geometries in triplet* 1,*n-biradicals.*



1 **2a-f** ***exo*-3a-f** ***endo*-3a-f**

Scheme 1. *Paternò-Büchi reaction with* 2,2*-dimethyl-*2,3*-dihydrofuran* (**1**).

Table 1. *Results of photolysis of* 2,2*-dimethyl-*2,3*-dihydrofuran with aldehydes.*

entry	R =	Conc. (M)	*endo/exo*-**3a-f**
A	Ph	0.1	86 : 14
B	o-Tol.	0.1	87 : 13
C	Et	1.0	62 : 38
D	Et	0.1	74 : 26
E	i-Pr	0.1	65 : 35
F	i-Bu	0.1	70 : 30
G	t-Bu	0.1	82 : 18

spin-orbit coupling controlled diastereoselectivity of the triplet photocycloaddition. In order to “block” the ring side of the cycloalkene, we introduced two methyl groups proximate to the oxygen atom of the 2,3-dihydrofuran substrate, i.e., at the C2-position.

2. RESULTS AND DISCUSSION

In this study, 2,2-dimethyl-2,3-dihydrofuran (**1**) was applied as a “ring-side blocked” substrate. This cycloalkene was prepared by a three step reaction according to a literature procedure [15]. In order to estimate if there is a correlation between spin selectivity and steric effects concerning the simple diastereoselectivity of the Paternò-Büchi reaction, the photocycloaddition of **1** with aliphatic and aromatic aldehydes was studied. As typical triplet carbonyl precursors, benzaldehyde (**2a**) and o-toylaldehyde (**2b**) were used. Additionally, four aliphatic aldehydes (**2c-f**) which can react either from their singlet as well as triplet excited states were irradiation with **1** in equimolar ratios in benzene (Scheme 1).

Both benzaldehyde and o-tolualdehyde, having high intersystem crossing (ISC) rates and thus exclusively reacting *via* their first excited triplet states with 2,2-dimethyl-2,3-dihydrofuran (**1**), showed high *endo/exo* selectivities (see Table 1, entries A and B, respectively). The selectivities were nearly identical to those with the unsubstituted 2,3-dihydrofuran as alkene component (88 : 12 and 90 : 10, respectively [16]).

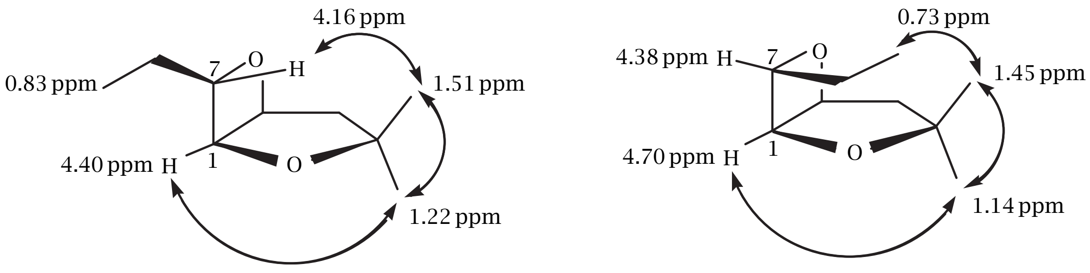
From recent concentration studies [3], we experienced that aliphatic aldehydes can equally react from both *singlet* and *triplet* excited states at specific concentrations (termed “isospin selectivity”). The photocycloaddition of the electronically excited propionaldehyde (**2c**) at high concentrations (1.0 M, singlet-like conditions) to 2,2-dimethyl-2,3-dihydrofuran (**1**) resulted in the oxetane **3c** with a moderate *endo/exo* selectivity (d.r.: 62 : 38) whereas the reaction at low concentrations of propionaldehyde (0.1 M, triplet-like conditions) showed an increase in *endo*-selectivity (d.r.: 74 : 26) (see Table 1, entry C and D). These values do not correspond to the spin-characteristic diasteroselectivities but are close to them, indicating that high *endo*-selectivity is characteristic to triplet photocycloadditions, whereas in case of the singlet excited carbonyl compounds, the diasteroselectivity approaches a 50 : 50 ratio.

The diastereomeric ratios for four different aliphatic aldehydes **1c-f** showed only marginal substituent effects, the *tert.*-butyl derivative (i.e., pivaldehyde **1f**) gave the highest *endo*-selectivities, contraintuitive from a ground-state point of view, but in agreement with the ISC-geometry model as shown in Figure 1.

The diastereomeric ratios of the oxetane-photoadducts were determined by ^{1}H-NMR spectroscopy and the product structures were identified from ^{1}H-NMR and ^{13}C-NMR spectral analyses. The relative configurations of the diastereoisomers *exo*-**3c** and *endo*-**3c** were unambiguously determined from NOE difference measurement. In the *exo*-**3c** isomer, irradiation of the methyl protons at 1.51 ppm led to nuclear Overhauser enhancements of both methyl protons signal at 1.22 ppm and the methine proton signal, H-7 at 4.16 ppm. Likewise, in *endo*-**3c**, irradiation of a methyl proton signal at 1.45 ppm led to nuclear Overhauser enhancement of the methyl signal at 1.14 ppm (see Figure 2).

3. MECHANISTIC ANALYSIS

The idealized structures for the triplet 1,4-biradical conformers prior to intersystem crossing (ISC) are shown in Figure 3.



***exo*-3c** ***endo*-3c**

Figure 2. *NOE interactions in bicyclic oxetanes exo-***3c** *and endo-***3c**.

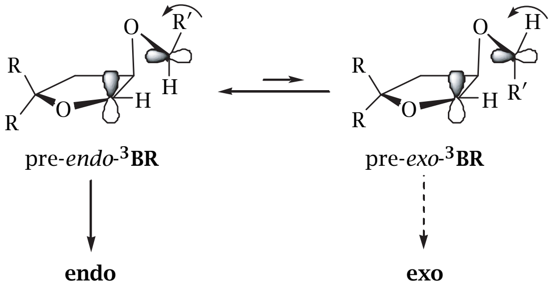


Figure 3. *Triplet* 1,4-*biradical precursors to diastereoisomeric oxetanes.*

Obviously, the most decisive interactions determining the product stereochemistry are between the α-hydrogen and the substituent R′ at C4 of the oxatetramethylene biradical. An increase in steric bulk of R′ is expected to lead also to an increase in the (thermodynamically less favoured) *endo*-diastereoisomer. This was verified for the *tert.*-butyl substituted oxetanes **3f** in comparison with the ethylated derivatives **3c**. Likewise, in the pure triplet photocycloadditions of **2a** and **2b**, the insertion of an *ortho*-methyl group led to an increase in *endo*-selectivity, i.e., an increase in population of the pre-*endo*-^{3}**BR**. On the other hand, two additional methyl groups at C-2 of the cycloalkene is not recognized in the critical biradical conformers and thus, does not alter the diastereoisomeric ratios.

4. CONCLUSION

The simple (non-induced) diastereoselectivity of the photocycloaddition of triplet excited aldehydes to 2,2-dimethyl-2,3-dihydrofuran (**1**) is high and contrathermodynamic (*endo*) due to the spin-orbit coupling controlled ISC geometries of the intermediary triplet 1,4-biradicals leading to ground state products (oxetanes **3**). By variation of the substrate concentration (spin mapping) the reactivity of the corresponding singlet excited carbonyls was estimated and shown to be considerably lower.

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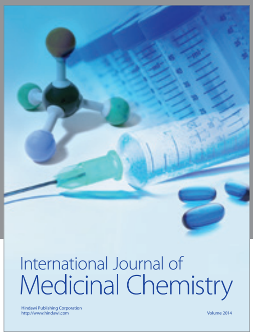
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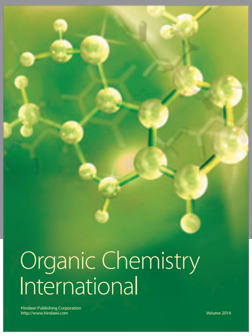
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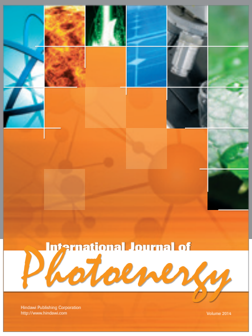
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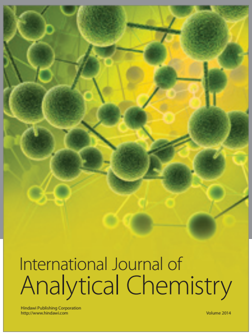
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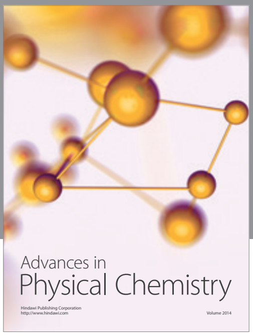
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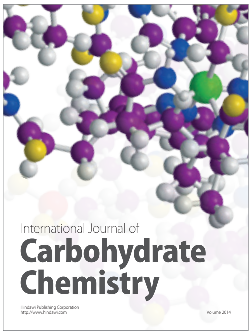
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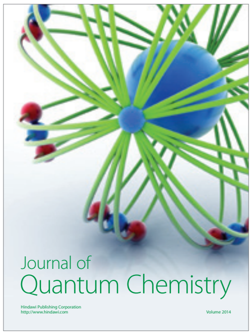
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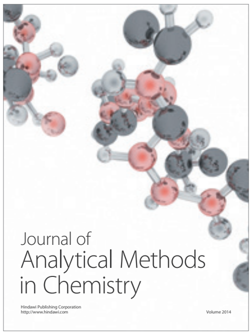
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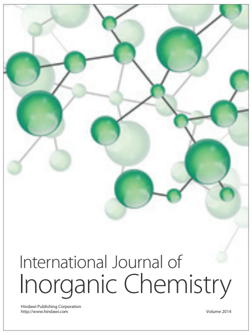
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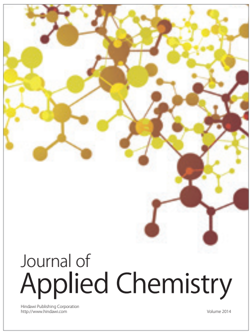
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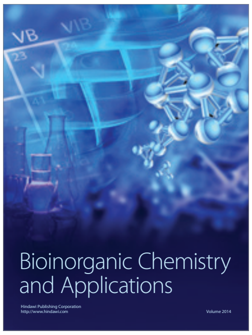
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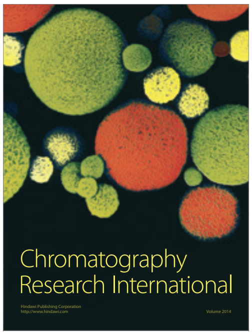
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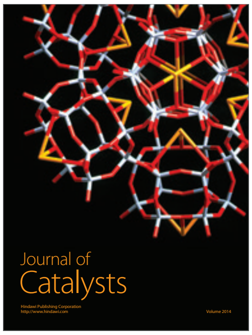
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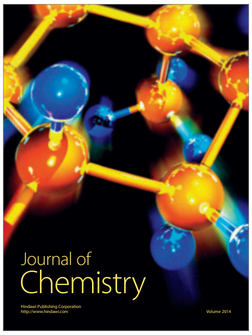
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