

Spin Photochemistry: Electron Spin Multiplicity as a Tool for Reactivity and Selectivity Control

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Abstract: Spin chemistry involving small organic molecules without heavy atoms is highly sensitive to spin-orbit-coupling (SOC) modulating biradical conformation as well as hyperfine coupling (HFC) modulating magnetic isotope interactions. Several easily available reaction properties such as chemo-, regio-, and diastereoselectivity as well as quantum yields serve as analytical tools to follow intersystem crossing (ISC) dynamics and allow titrating spin selectivities.

Keywords: Cycloaddition · Magnetic Isotope Effect · Photochemistry · Selectivity · Spin



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Seyma Bozkus received her Bachelor's and Master's degree in Chemistry (2013–2019) at the University of Cologne with a main interest in organic-, physical chemistry and biochemistry. She joined the Griesbeck research group during her Master studies on magnetic isotope effects in cycloaddition reactions and is now a PhD student as well as research assistant at the University of Cologne since 2020.

1. Introduction

This publication is dedicated to the memory of Thomas Bally, a wise and humorous colleague who passed away much too early in 2019. Thomas was a member of the Fribourg Chemistry Department, a colourful and stimulating group of chemists. I had always intense relations to some colleagues but do not exactly remember how this started. Probably with discussions with Edwin Haselbach during photochemistry conferences, common work on textbooks with Daniel Belluš, or on manuscripts with Thomas Bally or Christian Bochet. Many of them were interested in photo excitation processes and photochemistry and therefore I would like to present some ideas about specialities in photochemistry for an organic chemist. Thomas Bally has experimentally inves-

tigated reactive intermediates in photochemistry and the role of singlet/triplet species, *e.g.* carbenes and nitrenes,^[1] in his long career, and this is a great start for this paper. This made Thomas a specialist at the interface between mechanistic and synthetic photochemistry and his work always illustrative.

2. Background

Organic chemists are used to working preferentially in the dark, *e.g.* with electronic ground-state molecules and with closed-shell compounds; they were not used to working with open-shell molecules and with the unusual aspects of spin statistics. Recently, carbon radicals shifted more into the centre of numerous applications of photoredox chemistry and catalysis, either radical ions or uncharged radicals from photoinduced homolytic or mesolytic processes. In many cases, the typical reaction profiles and reaction selectivities can, however, be clearly deduced from closed-shell processes, because doublet/singlet interactions are spin-unrestricted. This situation fundamentally changes when triplet species come into the game.

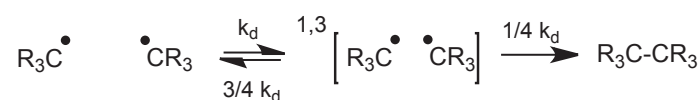
As an attractive term for these unexpected and often incomprehensible effects in photochemistry, 'spin chemistry' was introduced by N. J. Turro.^[2,3] This concept is used to describe the direct effects of electronic spins on the chemistry of electronic ground and excited states and their reactivity and selectivity.^[4] In materials chemistry and physics, this term is often used in the context of *spintronics* to describe effects at the supramolecular and materials science levels.^[5] The fundamental property of spin chemistry that we do not need in classical closed-shell reaction descriptions is the spin conservation law.

Thus, both bond-forming and bond-breaking processes are strictly spin-prohibited if they are coupled with a change in the spin multiplicity of a molecule or a set of strongly coupled molecules (a ground-state complex of two molecular units or an – electronically excited – exciplex). The vast majority of organic molecules exist in singlet electronic ground states (closed shell), and there are no spin constraints, either for unimolecular processes or for bimolecular reactions with other singular molecules. In radical addition to organic substrates in their singular electronic ground states, there are also no spin limitations, since doublet states are generated that can easily propagate in chain reactions. A variety of 1,n-biradicals (or diradicals)^[6] with triplet multiplicity are generated by triplet/singlet interactions in photochemical reactions. These triplet biradicals have been extensively studied both spectroscopically and theoretically in recent decades.^[7] They

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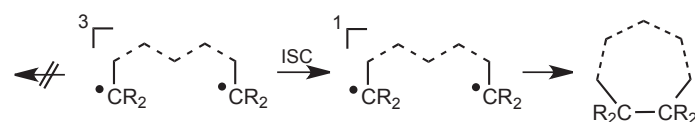
can be formed intramolecular as the first steps of photocyclization or intermolecular in photocycloadditions. These intermediates are the direct consequence of the spin of the precursor, and their lifetimes are related to the nature of the spin inversion process and the mechanism leading to the formation of closed-shell products. An interesting question is whether the sources of excited states that differ in their electronic spins also lead to different chemistry, *i.e.* different selectivities and reactivities.

Considering the trivial carbon radical interaction in a doublet/doublet collision complex (Scheme 1), the spin statistics show that direct C–C bond formation is not the preferred process. The Wigner spin rules describe the possible spin states that can be statistically achieved in such a molecular collision:^[8] The spin state of an interacting particle is given by $S = \sum s$ as the sum of the unpaired electron spins. An encounter complex AB of two particles with spin states $S_{A,B}$ can have the values $(S_A + S_B)$, $(S_A + S_B - 1)$, $(S_A + S_B - 2)$ $|S_A + S_B|$. In molecular collisions, the total electron spin angular momentum of the collision partners should not change even with weak spin-orbit coupling.^[9] As a consequence of this rule, the radical/radical encounter from two carbon radicals leads to either a singlet or triplet electronic spin state with $1/4$ vs. $3/4$ diffusion rate. The escape process regenerates the two independent radicals with 75% probability and product formation can only compete with 25%.



Scheme 1. Spin-dependent bond formation from singlet and triplet collision complexes.

In intramolecular versions of this process, radical escape diffusion is no longer possible and thus the lifetime of an initially formed triplet 1,*n*-biradical is determined by the rate of intersystem crossing (Scheme 2), provided that there are no other competing chemical pathways such as decomposition or further radical reactions. With weak spin-orbit coupling as the only intersystem crossing (ISC) driving interaction, long triplet biradical lifetimes can result, ranging from a few nanoseconds (for 2-oxatetramethylenes) to microseconds (for tetramethylenes).^[7,10]

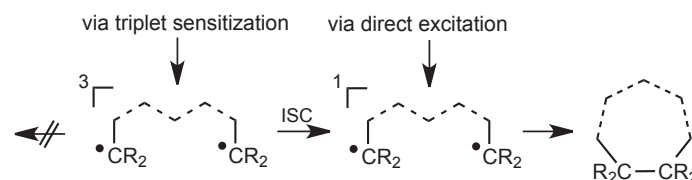


Scheme 2. Triplet/singlet 1,*n*-biradicals, intersystem crossing, and the steps to C–C-bond formation.

3. The Key Question in Organic Spin Photochemistry: Is Spin (Photo)chemistry Different?

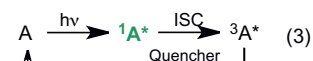
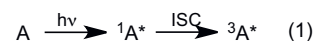
As shown in Scheme 3, the two reactive spin isomers are accessible either by direct excitation of a precursor molecule followed by a rapid biradical formation step (*e.g.* transfer of a hydrogen atom in Norrish II processes). Alternatively, triplet sensitization (*e.g.* in triplet energy transfer catalysis) is a routinely used method for generating reactive triplet biradicals, solely because direct excitation of precursor molecules is bypassed.^[11] This approach allows comparison of the chemical consequences resulting from the selective population of spin isomers. However, the reaction sequence shown in Scheme 3 suggests that both processes should ultimately lead to the same result, since the formation of

any closed-shell products from a triplet precursor requires ISC. Obviously, the final – and clearly irreversible – bond-forming step goes back to the same precursor species, regardless of its origin. But is this really so?



Scheme 3. Selective 1,*n*-biradical formation and direct/indirect product formation.

In photochemical reactions that are ideally suited for the generation of spin-isomeric radical intermediates, three experimental approaches can address this issue (Scheme 4). The sequence of electronic excitation and ISC allows the study of both reactive species simultaneously (1), while the selective generation of the triplet state ($^3A^*$) by sensitization with an external triplet sensitizer ($^3Sens^*$) bypasses ISC at the electronically excited molecule stage (2). This procedure allows the study of the photochemistry of the triplet state without the involvement of the energetically higher singlet excited state. The third approach (3) involves direct excitation of a molecule A in the presence of high concentrations of a specific triplet quencher reagent (Q). This approach recycles the excited triplet states and leads to the preferential formation of singlet-derived products. In all cases, the photochemistry studied here can be unimolecular from the excited singlet or triplet states or bimolecular. In the case of bimolecular reactions, the reactive ‘trap reagent’ (not shown in Scheme 4) maps the situation at the excited state level.



Scheme 4. Experimental approaches to study the different chemistry of biradical spin isomers.

A particularly interesting case occurs when the chemoselectivities of the singlet/triplet spin isomer reactions are identical, but the regio- and stereoselectivities of the product-forming steps are different. For singlet photoreactions, stereoselectivity is often controlled by the optimal geometries for radical-radical combinations, whereas for triplet photoreactions, the most favorable geometries for ISC are considered similarly relevant. These geometries may differ from the former due to differences in spin-orbit coupling values.^[11] These aspects play a crucial role in photochemical reactions for the synthesis of small ring products involving 1,4-biradicals, including the Paternò-Büchi reaction^[12] and Norrish–Yang photocyclization.^[13] Triplet 1,4-biradicals are crucial intermediates in triplet versions of these reactions. They have been detected by spectroscopy, trapping experiments, and radical clock experiments. The lifetimes of these species are on the order of nanoseconds to microseconds, and this is enough time for molecular motions, especially bond rotations, that are not normally available for their singlet spin isomers. Therefore, the conservation of specific substrate stereochemistry (conforma-

tions, configurations) in the transition from starting material to product is no longer expected for triplet photoreactions, and the stereochemistry of the products can be used as a simple tool to distinguish between these two reaction channels. Isomeric singlet biradicals have only been detected in the last two decades and are extremely short-lived unless strongly stabilized by *spin-diluting* substituents.^[14]

The lifetimes of many triplet biradical intermediates (e.g. trimethylenes, tetramethylenes, and 2-oxatetramethylenes) are long enough to allow bond rotations around C–C or C–X single bonds. Thus, the formation of the thermodynamically favoured products can be expected because the radical-radical combination step should no longer be affected by the approach geometry, *i.e.* *memory effects* should be cancelled out due to the relatively long lifetimes. On the other hand, the conversion of triplet biradicals into closed-shell products involves intersystem crossing, which is a spin-prohibited process and requires special geometry and energy conditions. These criteria were first described in the legendary publication by Salem and Rowland, who emphasized the role of spin-orbit coupling as a crucial interaction mechanism for triplet-to-singlet intersystem crossing in 1,n-biradicals.^[15] Unlike other interactions, such as electron-nuclei hyperfine coupling and spin-lattice relaxation, spin-orbit coupling depends strongly on the geometry of the triplet biradical. The rules that were postulated by Salem and Rowland are as follows: (i) spin-orbit coupling decreases with increasing distance between the two spin-bearing atoms. Because of additional through-bond interactions in the 1,n-biradical, the actual distance between the two radicals is important, but so is the number of bonds (n-1); (ii) conservation of total angular momentum requires that the axes of the p orbitals at the radical centers be orthogonally oriented to each other, and these axes must in turn be mutually orthogonal to the axes about which the orbital angular momentum is changed; (iii) spin-orbit coupling is proportional to the ionic character of the corresponding singlet biradical state. Summarizing these three rules, pronounced conformational and structural dependencies should emerge for the lifetime of triplet 1,n-biradicals. The numerical equation for spin-orbit coupling $\text{SOC} = B(R) |\text{S}| \sin \alpha$ has been proposed, in which $B(R)$ is the distance-dependent interaction function (R), $|\text{S}|$ is the radical overlap integral, and α is the dihedral angle between the radical p orbitals (Fig. 1).^[16]

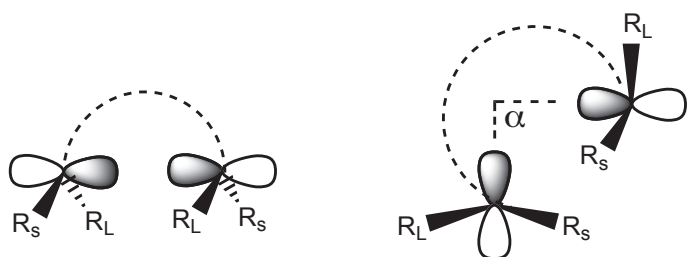
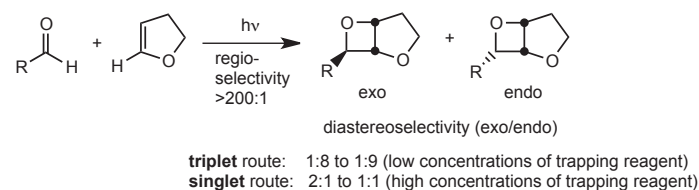


Fig. 1. Reactive geometries for C–C bond formation from singlet biradical spin isomers (left, steric repulsions avoided for large substituents R_L interactions) versus triplet biradical spin isomers (right, steric repulsions avoided in the more conformationally restricted orthogonal conformation, $\alpha = 90^\circ$).

When both singlet and triplet excited states of a chromophore behave comparably in a chemical reaction, the contributions of these spin isomeric states can be determined by *spin titration*, *i.e.* by changing the concentrations of the trapping reagent that interact with the singlet and triplet excited states with different rate constants. As an example of this approach, the diastereoselectivities of the singlet and triplet pathways were analyzed by the concentration dependence of Paternò-Büchi [2+2] photocyclo-

addition (Scheme 5). By direct absorption, aliphatic aldehydes generate excited singlet pathways with lifetimes of a few nanoseconds. ISC leads to the corresponding triplets with lifetimes in the microsecond range. Aromatic aldehydes have much higher ISC rates, so only the triplets are trapped with reagents in intermolecular reactions. These pure triplet Paternò-Büchi reactions, *e.g.* with benzaldehyde, show stereoselectivities of about 9:1 in favour of the *endo*-isomers. The singlet of aliphatic aldehydes, which can be trapped with large excesses of trapping reagents, show 1:1 selectivities, and the triplet in turn, shows high *endo* excesses (analogous to the reactions with aromatic aldehydes).



Scheme 5. Paternò-Büchi photocycloaddition of aldehydes to 2,3-dihydrofuran: regio- and diastereoselectivity.

Further increase of the trapping reagent DHF concentration leads to a 1:1 ratio of singlet and triplet state reactivity and this inflection point is characteristic for spin titration. The shape of these concentration/stereoselectivity correlations reflects the different kinetic contributions to this complex reaction scenario. The concentration dependence of the isobutyraldehyde/2,3-dihydrofuran (DHF) reaction is depicted in Fig. 2.^[17] At the concentration of 2,3-dihydrofuran at the inflection point, the contributions of the singlet and triplet states to product formation are equal. At low concentrations (triplet conditions), the diastereoselectivity approaches maximum *endo:exo* values of 90:10, and at high concentrations (singlet conditions), the diastereoselectivity decreases to 47:53.

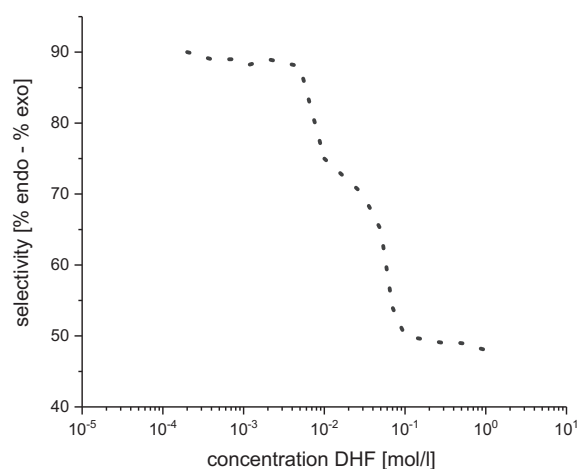
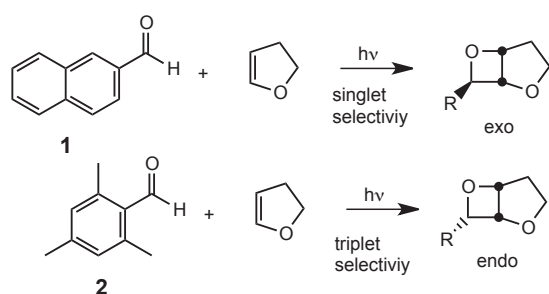


Fig. 2. Typical spin titration curve for the Paternò-Büchi reaction of 2,3-dihydrofuran (the trapping reagent) with isobutanal at 293 K in benzene.^[17] Selectivity (ordinate) refers to the *endo/exo* cycloadducts ratios.

Regardless of the mechanism for the corresponding *singlet* photoreactions, ISC conditions are irrelevant here. Thus, if singlet and triplet photocycloadditions with identical chemo- and regioselectivity are compared, the differences in the diastereose-

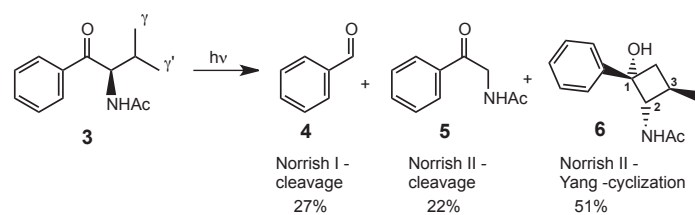
lectivities allow a conclusion about the role of ISC geometries. Another aspect of excited singlet and triplet states is the different state configuration. A well-known example (among dozens of other compound classes) are the naphthaldehydes (such as the β -compound **1**) that show 2+2-cycloaddition reactive $n\pi^*$ singlets and less reactive $\pi\pi^*$ triplets (Scheme 6). In this case, the Paternò–Büchi reactions are completely *exo*-selective (singlet spin reactivity) whereas the corresponding reactions of the $n\pi^*$ triplets of crowded benzaldehydes (such as the mesitylaldehyde **2**) are completely *endo*-selective (triplet spin reactivity).^[18]



Scheme 6. Comparison of singlet $n\pi^*$ and triplet $n\pi^*$ spin isomer selectivity.

3.1 More than one Triplet Product: Norrish I, Norrish II and Yang Cyclization

As shown in Scheme 7, the amino acid valine-derived butyrophene derivative **3** shows a divergent photochemistry with the three well-known primary and secondary carbonyl photo-pathways. Hydrogen atom transfer is preceding the formation of the cleavage product **5** as well as the cyclization product **6**.^[19] With respect to spin multiplicity, the Norrish II process is a typical triplet $n\pi^*$ initiated reaction whereas Norrish I has an appreciable singlet spin contribution. For this unimolecular case, the singlet/triplet distribution obviously cannot be measured by concentration effects. The major product, the cyclobutanol **6**, has three stereogenic centers; C2 is the substrate-specific center and C3 is generated through hydrogen transfer from one of the two diastereotopic γ -methyl groups (spin-independent). The stereogenic center C1, however, is generated after ISC of the initially formed 1-hydroxy-tetra-methylene biradical and thus sensitive to ISC-modulating effects. The high stereoselectivity (>98%) of the chiral induction with respect to C1-formation is therefore a signature of the rigid geometry for SOC-induced ISC, facilitated additionally by an intramolecular hydrogen bond between 1-hydroxy and 2-acetamido groups.



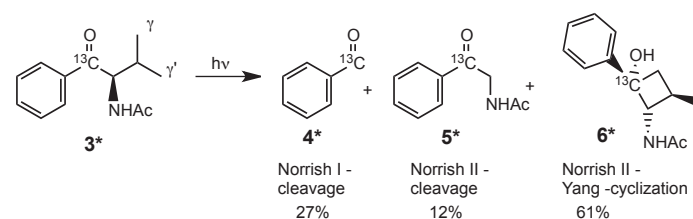
Scheme 7. Typical Norrish photochemistry of the valine derivative **3**: Norrish I, II, Yang cyclization.

3.2 More than one ISC Mechanism: Increasing HFC at the Expense of SOC: $^{12}\text{C}/^{13}\text{C}$ -Magnetic Isotope Effects

Classical isotopic effects (IE) observed in chemical reactions are usually associated with the influence of the isotop-

ic nuclear mass on the inertia moments and the vibrational frequencies of the respective molecule. Especially kinetic isotope effects (KIE) have been proven to be a powerful tool to elucidate reaction mechanisms. Isotopic effects can also occur due to differences in the isotopic magnetic properties of nuclei in radical reactions (the so-called magnetic isotope effect). If both electron and nuclear spin systems are coupled by hyperfine magnetic interactions (HFC), then the introduction of certain magnetic isotopes can influence the rate of ISC in radical pairs and thus offer an alternative spin-flip mechanism to the previously discussed SOC.^[20] Within the carbon isotopes, ^{12}C has the highest natural abundance and is non-magnetic. The ^{13}C isotope, on the other hand, has a spin quantum number of $1/2$ and as a result, also a magnetic moment. Thus a triplet radical pair (or a 1,*n*-biradical) containing ^{13}C should undergo more efficiently ISC in comparison to the ^{12}C isotope due to additional HFC contribution. This was verified in a number of publications reporting $^{12}\text{C}/^{13}\text{C}$ MIEs on radical pair decay kinetics and isotopic enrichment in micellar solutions.^[21]

With this in mind, a ^{13}C -label was introduced to the valine-derived butyrophene derivative **3*** at the carbonyl carbon and the photoproduct ratios were compared to the unlabelled substrate **3** (Scheme 8). While the Norrish I cleavage ratio remained the same in both labelled and unlabelled substrates (hints to a rapid singlet mechanism), a 20% increase in Norrish II-Yang cyclization product (**6***) and respectively a 20% decrease in Norrish II cleavage product **5*** formation could be observed with substrate **3***.

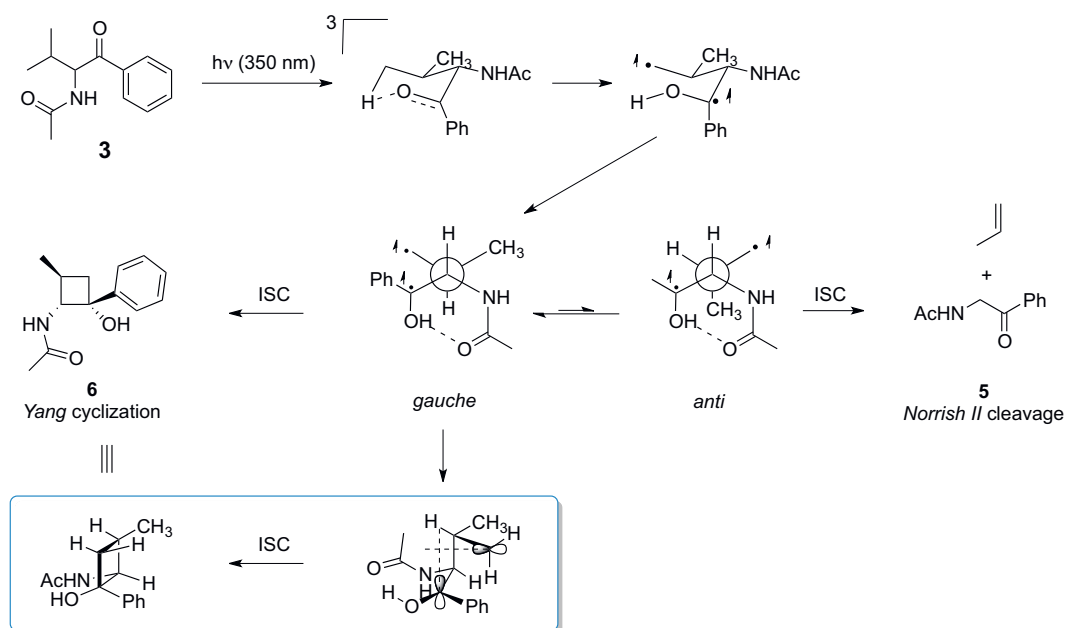


Scheme 8. Magnetic isotope effect with the ^{13}C -labeled valine derivative **3**.

To understand these changes in product ratios, the Norrish II reaction pathway from the triplet excited valine derivative **3** is highlighted in Scheme 9. After γ -hydrogen abstraction through a six-membered chair-like transition state with the methyl group preferentially in an equatorial position, the triplet 1,4-biradical is initially formed in a *gauche*-conformer. This biradical is in equilibrium with the (energetically less favoured) *anti*-conformer by rotation about the C2–C3 bond. It is widely accepted that after ISC, the singlet biradicals maintain conformational memory of their triplet precursors which means that the *anti*-1,4-biradical conformer results exclusively in cleavage products whereas the *gauche*-1,4-biradicals can cleave as well as cyclize.^[19] The introduction of the ^{13}C -isotope is expected to increase the ISC rate throughout the entire reaction scheme, however, because the *gauche* conformer is formed initially (and also stabilized by hydrogen-bonding), it is depleted/reacted further more rapidly and thus shifts the equilibrium between *anti* and *gauche* conformer towards the *gauche* conformer. Consequently, more Yang cyclization product is formed from the valine derivative with a ^{13}C -label. This effect is much beyond any ground-state $^{12}\text{C}/^{13}\text{C}$ -KIE.

4. Conclusion

The reaction parameters routinely used to analyze pericyclic reactions, such as overall relative rates, chemo-, regio-, and stereoselectivity, substituent and solvent effects, appear in a com-



pletely different light for photochemical reactions. Thermal activation barriers for rapid reactions are in the multi-kilocalories range whereas the coupling energies in SOC and HFC account for few calories or less and can completely dominate ISC processes. Conformational memory depicts these processes in the product configuration and thus allow spin mapping and the design of new reaction selectivities.

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