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Spin-Center Shift (SCS) – A Versatile Concept in Biological and Synthetic Chemistry

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Dedicated to Professor Bernd Giese

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Reactions involving radical intermediates are nowadays an inherent part of organic chemistry and the impressive progress in this area in recent decades has contributed to the understanding of many biological processes and provided many valuable methods for preparative chemists. By analyzing the mechanism of some biochemical transformations involving radical intermediates a common principle emerges. If at the atom adjacent to an α-hydroxy or α-alkoxy radical a leaving group is tethered a rapid elimination takes place and the spin density is shifted by one atom. This concept, called the spin-center shift (SCS), considerably extends the scope of some radical reactions. This microreview provides an overview of both biochemical examples of the SCS concept and synthetic applications.

1. Introduction

Chemical processes involving radical intermediates are nowadays well-established in organic synthesis and numerous applications have been published in recent years.[1] Furthermore, radicals play an important role in physiological chemistry.[2] Thus, there are many biochemical pathways comprising radical species, for example, the biosynthesis of deoxyribonucleotides (cf. section 2.1). On the other hand, many degenerative processes are also related to radicals, for example, DNA damage caused by oxidative stress (cf. section 2.3).

Leaving aside redox reactions involving metals and metal cations, the reactions of radicals can be roughly subdivided into those destroying radical character and those preserving it. The two most important radical-destroying reactions are radical recombination and disproportionation. Reactions that preserve radical character are rearrangement, addition,

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Pablo Wessig, born 1962 in Görlitz, Germany, completed his Ph. D. at the Humboldt University of Berlin under the supervision of Prof. H.-G. Henning in 1990. After a postdoctoral research fellowship (FCI) at the University of Basel, Switzerland, working in the group of B. Giese (1993) he attended the Habilitation working in the group of G. Szeimies at the Humboldt University (2000). Since 2003 he has worked as the Heisenberg fellow of the DFG at the same university. His primary research interests are focused on preparative organic photochemistry, molecular probes, and rigid molecular sticks.

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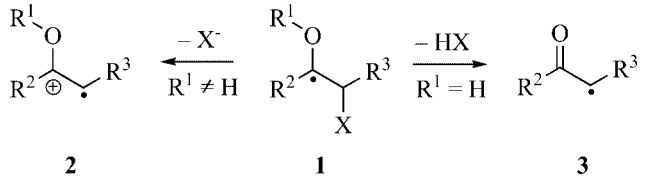
and elimination reactions. In all these reactions the position of the radical center is shifted to another atom in the course of the reaction. Looked at in this way, these reactions can be regarded as spin-center shift reactions in the broadest sense.

Of the various types of elimination reactions of radicals that are known, one process plays a particularly important role in both a biochemical and synthetic context. It is based on the elimination of a leaving group (or the corresponding acid) located at the atom adjacent to the radical center. This process is strongly facilitated if a hydroxy or an alkoxy group is tethered at the radical center. Thus, radicals **1** undergo very rapid elimination either to radical cations **2** or to oxoallyl radicals **3** depending on the functional group at the radical center. In both cases the spin density is shifted to the adjacent atom (Scheme 1). We define the reactions summarized in Scheme 1 as spin-center shift reactions in the narrowest sense (SCS) and this is the topic of this review.



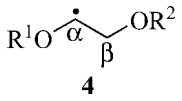
2 **1** **3**

Scheme 1. The concept of spin-center shift reactions in the narrowest sense (SCS).

First, we will demonstrate that the concept of SCS is not actually an invention of synthetic chemists but is process widely disseminated in nature. Accordingly, three biochemical processes related to SCS reactions will be presented in section 2. Deoxyribonucleic acid (DNA) is surely the most important biomolecule and, interestingly, SCS reactions are involved in the biosynthesis of DNA (section 2.1) and in the pathogenic DNA damage caused by radicals (section 2.3). Current knowledge about the mechanism of the SCS reaction is summarized in section 3. Finally, we report on various synthetic applications of the SCS reaction, both in monoradical chemistry (section 4.1) and in the chemistry of photochemically generated diradicals (section 4.2). The latter topic is closely related to one of the most important photochemical reactions, the Norrish–Yang reaction, and the examples presented in this section stem mainly from our own research.

2. Spin-Center Shift Reactions in Biochemical Processes

Spin-center shift reactions are important key steps in several radical-induced biological processes. In this context, radicals of general structure **4** play an important role (Figure 1). These α,β-dioxyalkyl radicals can be detected in different enzyme-catalyzed reactions[3] and in the destruction of DNA.[4]



4

Figure 1. α,β-Dioxyalkyl radical **4**.

2.1. Synthesis of DNA: Deoxygenation of Ribonucleotides

Carbohydrate-based radicals, structurally related to α,β-dioxyalkyl radicals **4**, are involved in both the formation and the destruction of DNA.

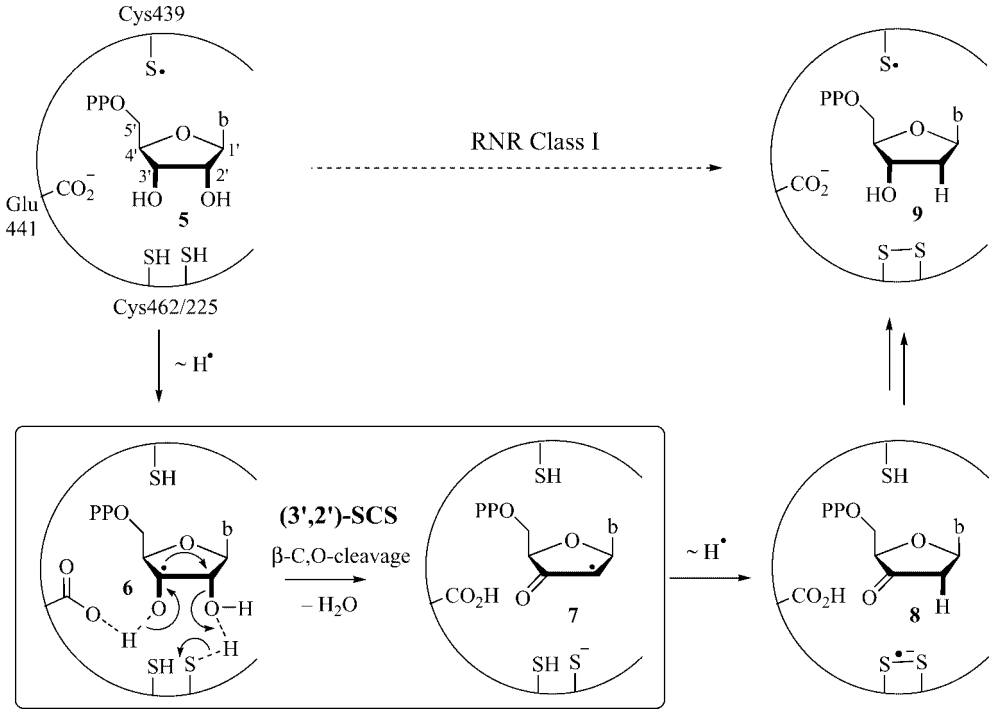
Deoxyribonucleoside diphosphates (dNDPs) **9**, the monomeric precursors of DNA, are formed in the radical deoxygenation of ribonucleoside diphosphates (NDPs) **5**. This conversion is catalyzed by the enzyme ribonucleotide reductase (RNR Class I–III) in all organisms.[5] Different mechanisms for this process have been discussed in recent years;[5b,6] a recent abbreviated version of the RNR Class I mechanism is shown in Scheme 2. The first step is a homolytic cleavage of the C3′–H bond by a thiyl radical (Cys439) giving an α,β-dioxyalkyl radical **6**, more precisely a 3′-ribonucleotide radical (**5**→**6**). This reactive intermediate is the starting point for a (3′,2′)-SCS (**6**→**7**): The glutamate at position 441 abstracts a proton from the C3′–OH group of the substrate. Simultaneously, as suggested by theoretical studies,[7] the hydroxy group at C2' is protonated by a cysteine (Cys225), leading to both β-C–O cleavage and the elimination of water. On the basis of experiments with model compounds, mechanisms involving either a radical cation or a radical anion have been discussed for this step (**6**→**7**), but a completely concerted mechanism is currently favored.[6,7] In the next step (**7**→**8**), the C2′ atom of the oxoallyl radical **7** abstracts a hydrogen atom from a second cysteine (Cys462) and the two cysteines form a disulfide radical anion. Further reactions lead to the formation of the deoxyribonucleotide **9**.

2.2. Inactivation of Ribonucleotide Reductase

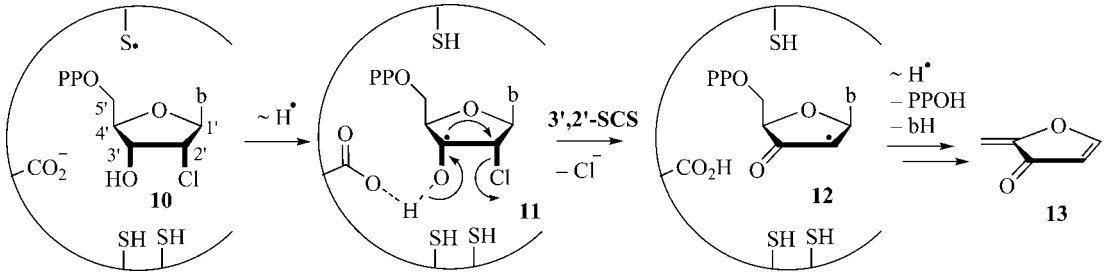
Substrate analogues of ribonucleoside diphosphates can initiate reactions that lead to the inactivation of the enzyme ribonucleotide reductase (cf. section 2.1).[8] Most of the substrate analogues differ from the NDPs by the nature of the functional group X located at the C2′ position (2′-X-dNDPs: X = Cl, N_3, F, CN). Similar to the reduction of natural substrates, the mechanism for RNR inactivation by 2′-Cl-dNDPs **10** starts with a hydrogen atom abstraction from C3′ (Scheme 3, **10**→**11**). Deprotonation of the C3′–OH group by Glu441 and spontaneous loss of chloride together with a (3′,2′)-SCS gives oxoallyl radical **12** without involvement of the cysteine pair (Cys462/225). This means the catalytic cycle is disturbed significantly: The ketone intermediate fails to be reduced. Instead, two β-elimination reactions give a reactive Michael acceptor **13** that can effect covalent inactivation of the enzyme RNR.

2.3. Damage to DNA by Oxidative Stress

DNA can be damaged either at the nucleobases[9] or at the sugar moieties.[4a] Damage of the deoxyribose moiety

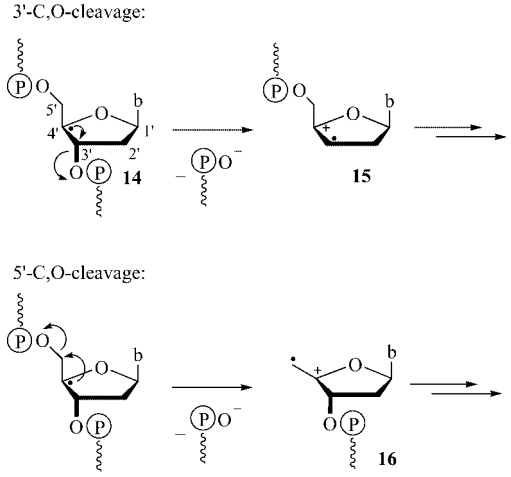


Scheme 2. Mechanism for the RNR Class I reaction.



Scheme 3. Inactivation of RNR via 2′-Cl-dNDPs.

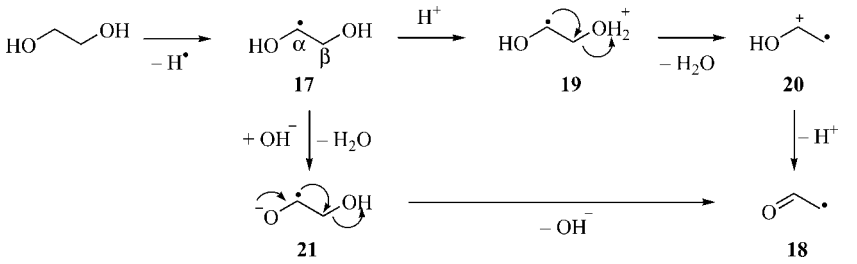
initiated by hydrogen abstraction can lead to the loss of a nucleobase and/or to DNA single-strand cleavage. An α,β-dioxyalkyl radical of type **4** may be generated if the hydrogen abstraction occurs from the C3′, C4′, or C5′ position of the sugar moiety. For every position, with the exception of C4′, decomposition mechanisms have been discussed in which the first radical generated reacts with oxygen (aerobic conditions) or with water (anaerobic conditions). The 4′-DNA radical **14** occupies an exceptional position: Groundbreaking investigations by Schulte-Frohlinde[10] and later by Giese[11] demonstrated that under anaerobic conditions heterolytic β-C–O cleavage is preferred over radical trapping reactions. As shown in Scheme 4, enol ether radical cation **15** (C3′–O cleavage) or **16** (C5′–O cleavage) arises from **14**.[12] Quantum chemical calculations using a model compound have shown that the spin density is located predominantly at the adjacent C3′ position.[13] In other words, a spin-center shift occurs.



Scheme 4. DNA strand cleavage via 4′-DNA radicals under anaerobic conditions.

3. Mechanistic Background

In section 2.1 we demonstrated that under enzymatic conditions (acid and base catalysis) α,β-dihydroxyalkyl radicals can undergo β elimination of water to generate an



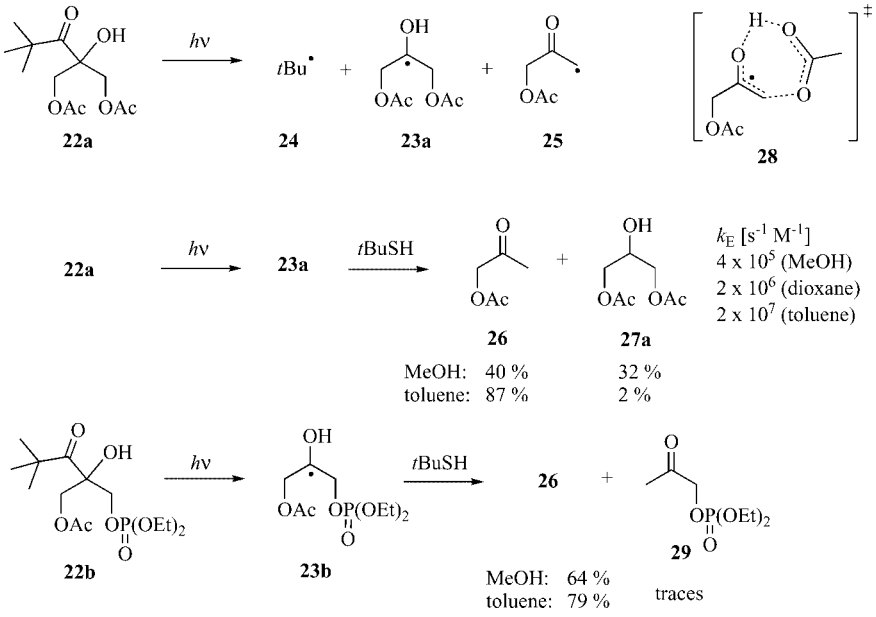
Scheme 5. Mechanism for the β elimination of water from α,β-dihydroxyalkyl radicals.

oxoallyl radical. As early as the 1960s and 1970s several groups, using ESR spectroscopy[14] or γ radiolysis,[15] recognized that under more strongly acidic conditions an α,β-dihydroxyethyl radical **17** (generated from ethylene glycol) rapidly rearranges to the formylmethyl radical **18** (Scheme 5). Concerning the mechanism, the rough consensus of opinion was that the oxoallyl radical **18** was formed by protonation of the β-hydroxy group of the initial radical **17** (**17**→**19**), followed by elimination of water (**19**→**20**) and deprotonation (**20**→**18**). However, this fragmentation should also be possible under basic conditions starting with the deprotonation of the α-hydroxy group (**17**→**21**). Indeed, Lens and Giese found in studies on the mechanism of the RNR-catalyzed reduction of deoxyribonucleoside diphosphates that under neutral conditions the fragmentation is subject to general base catalysis.[16] Owing to the strong acidity of α-hydroxyalkyl radicals,[17] α-OH deprotonation occurs much faster than β-OH deprotonation.

Anyhow, it is generally accepted that in the absence of acid or base catalysis (neutral aprotic conditions) this fragmentation of α,β-dihydroxyalkyl radicals will usually not be observed.[18] Further investigations by Giese and co-workers[19] have shown that spontaneous elimination under neutral aprotic conditions requires a better leaving group in the β position.

To find evidence for radical-induced lipid damage, Giese and co-workers, amongst others, investigated the chemical behavior of α-hydroxyglyceryl radicals **23** by ESR spectroscopy, product analysis, and kinetic measurements (Scheme 6).[19] The corresponding *tert*-butyl ketones **22** were used as photolabile precursors for these radicals bearing an acetate (**23a**) or phosphate group (**23b**) in the β position.

Upon irradiation of **22a** in benzene, three radicals could be observed by ESR spectroscopy: The *tert*-butyl radical (**24**), the α-hydroxyalkyl radical **23a**, and the oxoallyl radical **25**. Preparative-scale photolysis of **22a** in toluene and in the presence of *t*BuSH as hydrogen donor yielded ketone **26**, the product of acetic acid elimination, as the major product (87%) and only 2% of the reduction product **27a**. In methanol, **26** and **27a** were formed in 40 and 32% yields, respectively. Competitive kinetic measurements in solvents of different polarity (methanol, dioxane, and toluene) allowed the rate constants for acetate elimination from radical **23a** to be determined. As a result, the elimination reaction increased by a factor of 50 on going from methanol to toluene. This solvent dependence is strong evidence for a concerted mechanism in which α-hydroxyalkyl radical **23a** is directly transformed into oxoallyl radical **25** via a cyclic, hydrogen-bonded transition state. Ab initio calculations



Scheme 6. Chemical behavior of α-hydroxyglyceryl radicals **23**.

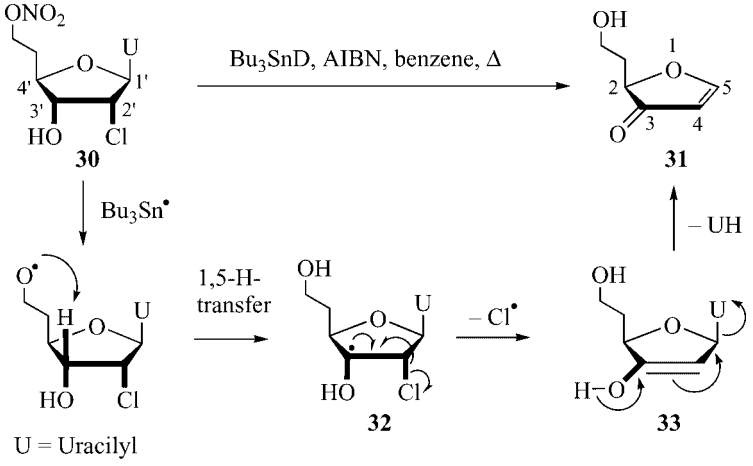
indicated a seven-membered transition state **28** with a hydrogen bridge between the carbonyl oxygen atom of the leaving group and the α-OH group. In methanol and dioxane, hydrogen bridging between the solvent and the oxoallyl radical disfavors the cyclic transition state, thus reducing the rate of elimination.

Photolysis of ketone **22b** led to the generation of α-hydroxyalkyl radical **23b** in which elimination of acetate and diethyl phosphate compete. Even in the presence of the hydrogen donor *t*BuSH, ketone **26**, which is formed through diethyl phosphate elimination, was almost exclusively obtained. No reduction product was found and only traces of ketone **29** resulting from β elimination of acetate. Thus, the rate of β elimination also depends on the "quality" of the leaving group. In earlier investigations, Giese et al. found a correlation between the elimination rate and the pK_a of the conjugate acid of the leaving group: The stronger the conjugate acid the higher the rate of β elimination.[11b]

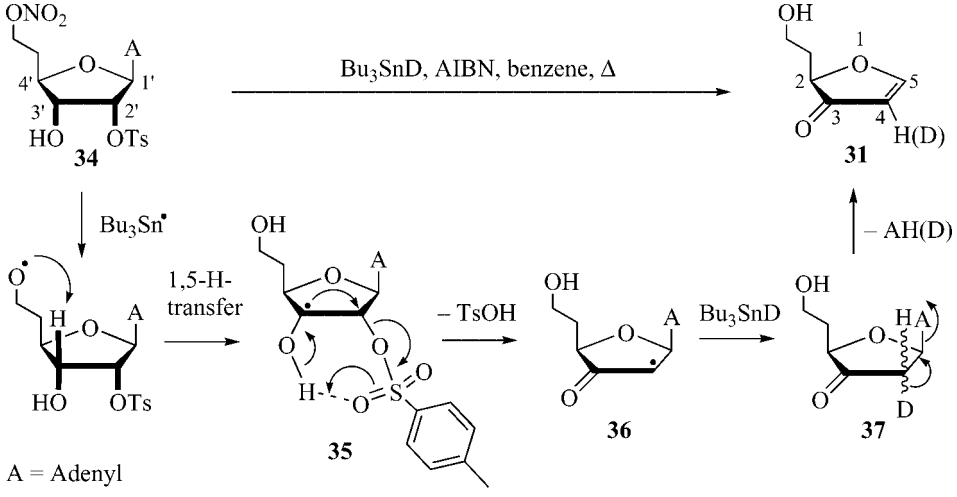
From the biomimetic simulation experiments of Robins and co-workers we can derive important information concerning the mechanism of β elimination depending on the nature of the leaving group (Cl vs. OTs).[20] For RNR inactivation by 2′-Cl-dNDPs (cf. section 2.2), Robins and coworkers favor chlorine radical elimination, that is, treatment of 6′-*O*-nitro ester **30** with Bu_3SnD and AIBN at elevated temperatures led to the formation of a deuterium-free furanone **31** (Scheme 7). As a consequence of chlorine radical elimination (**32**→**33**), no oxoallyl radical is formed but an enol **33** from which furanone **31** results after 1,4-elimination of UH (**33**→**31**).

In contrast, conversion of the analogous 2′-*O*-tosyl compound **34** under the same conditions gave **31** with around 30% deuterium incorporation at C4 (Scheme 8). This is strong evidence for a concerted mechanism for *p*TsOH elimination (**35**→**36**) similar to that reported by Giese.[19] The resulting oxoallyl radical **36** receives a deuterium atom from Bu_3SnD preferentially at the less hindered α face to give compound **37** [C2′, (*R*)/(*S*) = ca. 30:70]. In the last step **37** undergoes *anti* 1,2 elimination to give **31** with around 30% deuterium remaining at C4.

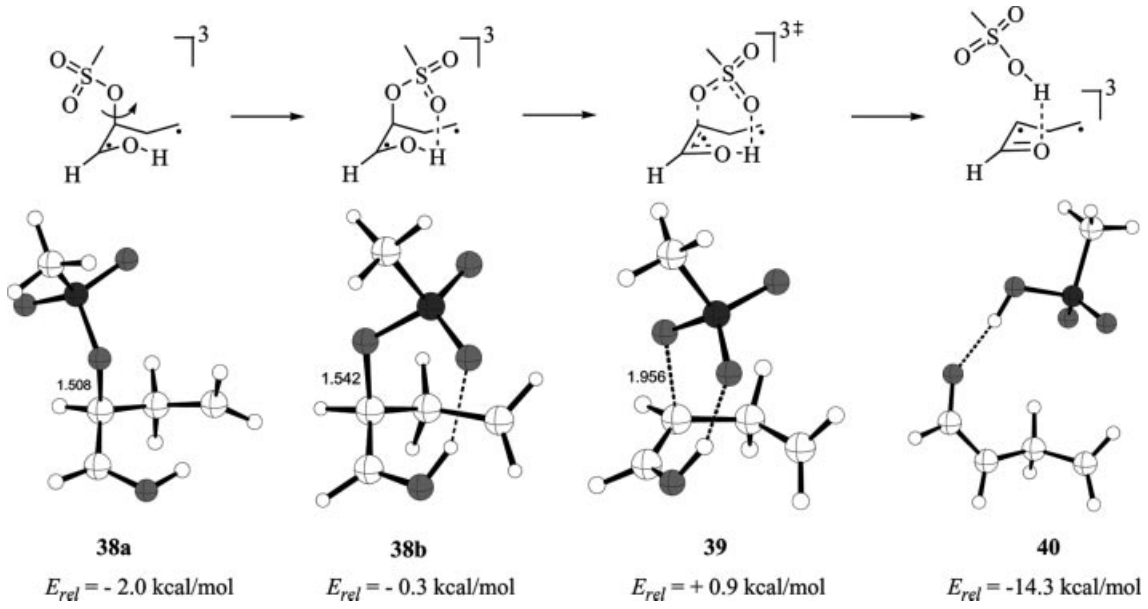
The conclusions of Giese [concerted elimination of $HOPO(OEt)_2$ and HOAc] and Robins (concerted elimination of *p*TsOH) for the SCS mechanism are in good agreement with our own results: To clarify the mechanism



Scheme 7. Radical mechanism for chlorine elimination (**32**→**33**).



Scheme 8. Concerted mechanism for *p*TsOH elimination (**35**→**36**).



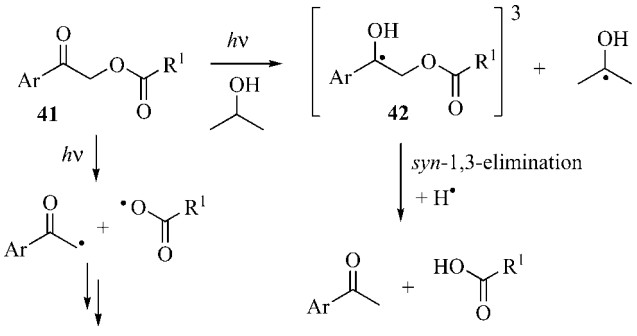
Scheme 9. Concerted mechanism for MsOH elimination from triplet diradical **38** (B3PW91/6-311++G**//B3PW91/6-31G*).

of our novel photochemical cyclopropane synthesis (cf. section 4.2.1) we performed comprehensive DFT calculations (B3PW91/6-311++G**//B3PW91/6-31G*) on 2-mesyloxybutanal as a model system (Scheme 9). In the course of this reaction a triplet α-hydroxy-β-mesyloxy diradical **38** is generated which undergoes elimination of MsOH to give an oxoallyl diradical. This triplet diradical may be converted from conformer **38a** to another conformer **38b** by rotation around the C–O(Ms) bond. From an energetic point of view conformer **38b** is slightly less favorable (ΔE = 1.7 kcal/mol). However, an intramolecular hydrogen bridge between the S=O oxygen of the leaving group and the α-OH group in **38b** indicates the subsequent elimination of MsOH via transition state **39**. Consequently, the C–O(Ms) bond in **38b** is stretched significantly compared with that in **38a** (1.542 vs. 1.508 Å). MsOH elimination occurs through a very low activation barrier of 1.2 kcal/mol giving the hydrogen-bonded complex **40** formed between the oxoallyl diradical and MsOH.

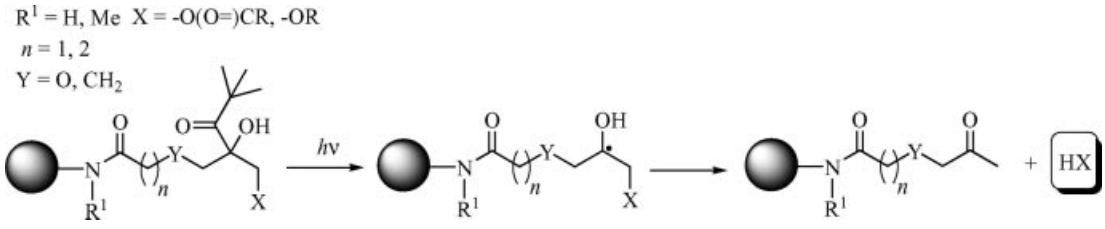
4. Synthetic Applications

4.1. "Monoradical" Applications

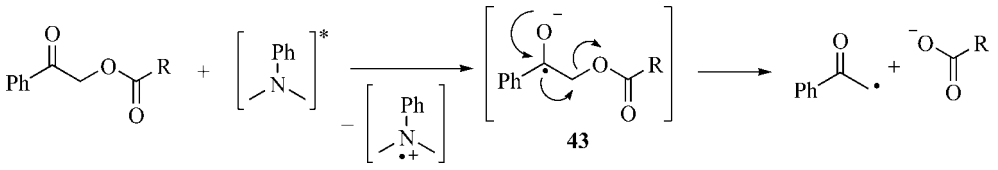
Giese and co-workers have developed a photolabile linker for the solid-phase synthesis of carboxylic acids (HX = RCO_2H) and alcohols (HX = ROH) based on their work on the chemical behavior of α-hydroxyglyceryl radicals (cf. section 3).[21] The photochemically induced release of HX is a two-step process (Scheme 10): An α-hydroxy-β-X-alkyl radical is generated through a Norrish Type I cleavage, followed by spontaneous β-C–X cleavage and release of HX. Interestingly, this concept is also useful for ether cleavage although alcoholates are normally bad leaving groups. However, for efficient cleavage of ethers a slightly acidic medium (ca. pH 5.5) is necessary.[21b]



Scheme 11. Photochemically induced carboxylic acid release from phenacyl esters.



Scheme 10. A photolabile linker for the solid-phase synthesis of carboxylic acids and alcohols.



Scheme 12. Mechanism for carboxylic acid release from phenacyl esters by PET.

Phenacyl chromophores are useful photochemically removable protecting groups for carboxylic acids (Scheme 11).[22] Concerning the mechanism of carboxylic acid release from phenacyl esters, it is proposed that upon direct photolysis and in the absence of an appropriate hydrogen donor, β-C–O bond homolysis is involved.[23] Banerjee and Falvey found that in the presence of *i*PrOH as hydrogen donor the initial step is an intermolecular hydrogen atom transfer between *i*PrOH and the photochemically excited ketone **41** giving an α-hydroxyalkyl radical **42** from which the carboxylic acid is released via a seven-membered transition state (cf. Scheme 6). However, based on laser flash photolysis experiments Falvey postulates a different mechanism for the carboxylic acid release.[24]

As an alternative to the direct excitation of the phenacyl chromophore, cleavage of the phenacyl group can be initiated via a photochemically induced electron transfer (PET).[25] Here, the phenacyl group receives an electron from an appropriate electron donor (e.g., singlet excited *N*,*N*-dimethylaniline, $h\nu$ = 332 nm) leading to a radical anion of structure **43** which releases the carboxylate anion (Scheme 12).

4.2. "Diradical" Applications: The Concept of Spin-Center Shift

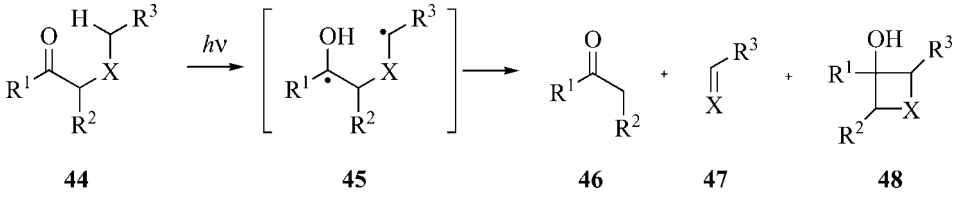
The chemistry of diradicals, that is, reactive intermediates bearing two radical centers, differs from that of monoradicals in some respects. In contrast to monoradicals, the spin multiplicity of diradicals (singlet or triplet) must be taken into consideration. A second peculiarity of diradicals is that their lifetimes are often shorter by more than three orders of magnitude than monoradicals.[26] Although the generation of diradicals by thermal processes is possible in principle,[27] most of the preparative procedures are based on photochemical reactions. Two diradical-generating photochemical reactions have been particularly well investigated: the Paterno–Buechi reaction[28] and the Norrish–Yang reaction.[29] Most of the examples discussed in this section are SCS extensions of the latter reaction.

In 1934, Norrish and Appleyard observed upon irradiation of aliphatic ketones **44** (R^1 = alkyl, X = C[sp^3]) a cleavage reaction providing ketones **46**, whose alkyl chain was cleaved between the α- and the β-carbon atom with respect to the carbonyl group, and alkenes **47**.[30] Nowadays, this cleavage reaction is named the "Norrish Type II cleavage". Certainly as a result of the limited analytical capabilities of 70 years ago, Norrish and Appleyard did not find the second group of products formed by the same initial process, namely, cyclization products. Yang and Yang recognized in 1958 the formation of cyclobutanes **48** in addition to the Norrish Type II cleavage products **46** and **47**.[31] This discovery formed the basis of a very versatile and valuable ring-closure reaction that was termed the "Norrish–Yang reaction". The occurrence of diradicals **45** as key intermediates is an important feature of this reaction (Scheme 13).

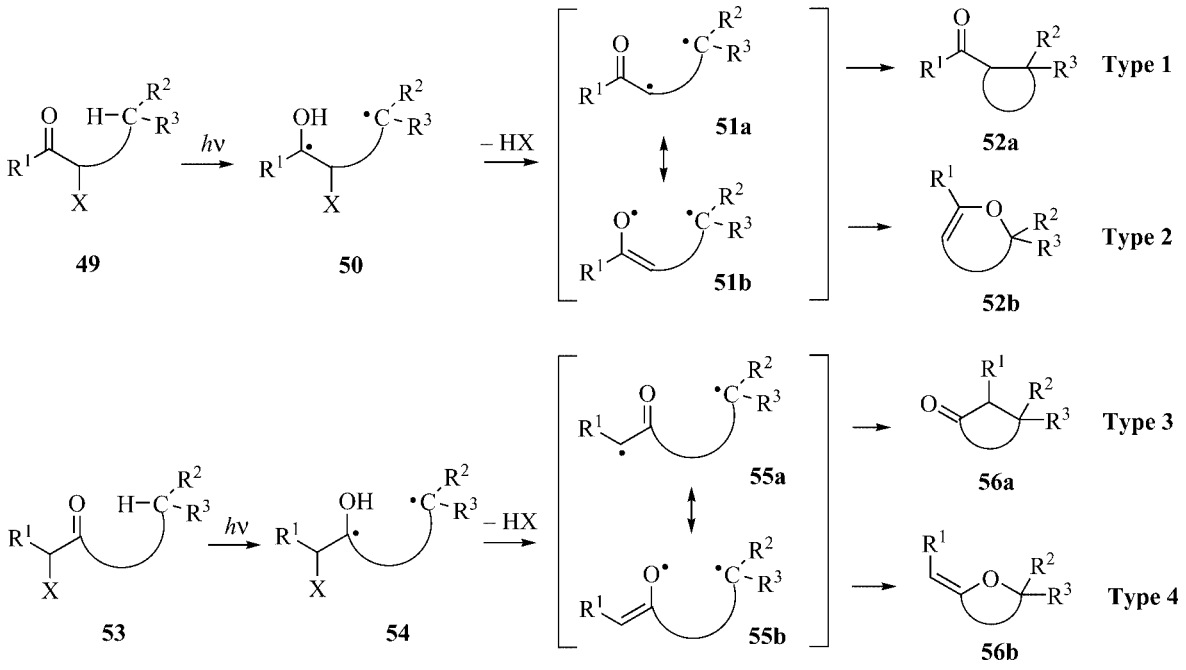
Depending on the linking group X, a variety of carbo- and heterocyclic compounds have been prepared by means of the Norrish–Yang reaction. Accordingly, cyclopropanes, cyclobutanes (the Yang reaction in the narrowest sense), azetidines, oxetanes, cyclopentanes, pyrrolidines, tetrahydrofurans, cyclohexanes, piperidines, quinolines, chromanes, and some macrocyclic compounds were obtained in this way.[32]

Recently, we developed a valuable extension of the Norrish–Yang reaction[33–35] based on a phenomenon that is well known for hydroxy-substituted monoradicals bearing a leaving group at the adjacent carbon atom. (cf. section 4.1). These radicals are subject to a very rapid acid elimination to provide oxoallyl radicals. The decisive feature of this elimination process is the shift in the spin density of the radical by one atom. Applied to the diradicals formed in the course of the Norrish–Yang reaction, the number of atoms linking the two radical centers is altered and, consequently, the size of the ring formed after the combination of the radical sites. In the following explanations we denote this concept as the spin-center shift extension of the Norrish–Yang reaction (SCS-NY).

Depending on the position of the leaving group, two reactant types **49** and **53** can be distinguished, the photo-



Scheme 13. The Norrish–Yang reaction.



Scheme 14. Different types of SCS-NY reactions.

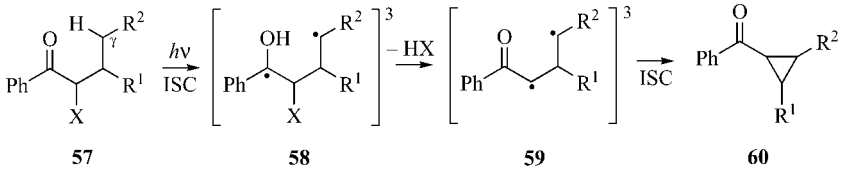
chemical reactions of which are summarized in Scheme 14. With reactant **49**, the leaving group is attached to an atom of the chain between two reaction centers, whereas with reactant **53**, the leaving group is tethered to an atom beyond the carbonyl group. The diradicals **51** and **55** formed after the elimination step can be considered both as C–C diradicals, **51a** and **55a**, respectively, and as O–C diradicals, **51b** and **55b**, respectively. The following sections will demonstrate that all of the carbocyclic (**52a**, **56a**) and heterocyclic (**52b**, **56b**) products may be selectively prepared depending on the structure of the reactants (Scheme 14).

4.2.1. Cyclopropanes (SCS-NY Type 1)

The precondition for the synthesis of cyclopropanes as products of a Norrish–Yang reaction is the formation of 1,3-diradicals and consequently a hydrogen abstraction from the β position with respect to the carbonyl group. The geometrical parameters of the corresponding five-membered transition state, especially the O–H–C bond angle, differ substantially from the ideal parameters reported by Scheffer and co-workers.[36] Therefore, it is not surprising that only a few syntheses of cyclopropanes through the Norrish–Yang reaction are known.[37–39] In most of these cases, it was either proven or considered to be very likely that the initial step is a photoinduced electron transfer (PET). In addition, the hydrogen atom is transferred not homolytically, but by a proton shift after PET. These conditions limit the preparative scope of the reaction because the electron-rich functional groups responsible for PET render the cyclopropanes considerably sensitive to oxidative ring-opening.

This situation was substantially improved by the utilization of the SCS concept in the synthesis of cyclopropanes.[33] The reactants for cyclopropane synthesis by SCS-NY are alkyl aryl ketones **57** bearing a leaving group X at the atom adjacent to the carbonyl carbon atom. Upon irradiation, hydrogen migration from the γ position to the carbonyl oxygen atom takes place after intersystem crossing (ISC), giving the 1,4-diradical **58**. If the leaving tendency of X is too low [e.g., X = OC(=O)R, Cl], the products of the Norrish–Yang reaction (cleavage and cyclization) are mainly formed from **58**,[40,41] whereas with X = Br, homolytic C–Br bond cleavage is observed.[41] In the case of good leaving groups such as sulfonates and nitrates, very rapid elimination of acid HX takes place and 1,3-diradicals **59** are obtained that cyclize to cyclopropanes **60** after repeated ISC to the singlet state (Scheme 15).

A common feature of all preparative SCS reactions is the formation of strong acids HX during the irradiation process. In the presence of these acids benzoylcyclopropanes **60** are not stable upon irradiation, but undergo rapid ring-opening. Consequently, an efficient acid scavenger must be



Scheme 15. Cyclopropane synthesis by the SCS-NY reaction.

added and we found that imidazole or *N*-methylimidazole (NMI) is best suited to this purpose. The reaction outlined in Scheme 15 is very versatile and tolerates many functional groups. The yields of a selection of cyclopropanes **60** are summarized in Table 1.

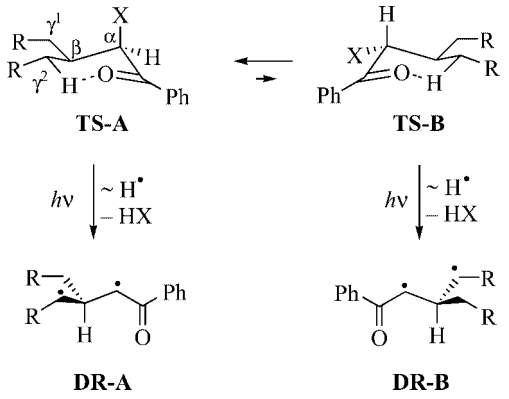
Table 1. Yields of cyclopropanes **60a**–**e**.[a]

60	R^1	R^2	X	Yield [%]
a	H	H	OMs	87
b	Me	H	OMs	90
c	H	Ph	OMs	78
d	H	CN	OMs	65
e	H	*c*Pr	OTs	68

[a] Conditions: DCM/NMI (2 equiv.).

The formation of compound **60e** bearing a cyclopropyl group allows conclusions to be drawn about the lifetimes of diradicals **58** and **59**. It is widely known that cyclopropylcarbinyl radicals undergo very rapid ring-opening ($k = 4.0 \times 10^7\ s^{-1}$) and this reaction has often been utilized in the determination of radical lifetimes.[42] Consequently, the formation of bicyclopropyl ketone **60e** in 68% yield and without any indication of opening of the terminal cyclopropyl ring proves that the sum of the lifetimes of the primarily formed 1,4-diradical **58** and 1,3-diradical **59** is considerably smaller than 25 ns.

Quantum chemical calculations on the cyclopropane formation revealed an interesting peculiarity in the reaction mechanism. Thus, owing to a hyperconjugative interaction between the C–X σ bond and the semi-filled π orbital of the excited carbonyl group, the reactants **57** prefer conformation **TS-A** in the initial hydrogen transfer step in which the leaving group is arranged pseudoaxially with respect to the cyclic transition state. This phenomenon gave us the idea of developing an entirely new stereoselection principle based on a 1,2-chirality transfer.[33c] The principle of this approach is portrayed in simplified terms in Scheme 16. If two identical groups R–CH_2 are tethered at the β position, this atom may be regarded as the prochiral center and the positions γ^1 and γ^2 are diastereotopic. On the basis of the preference for the **TS-A** conformation, the excited carbonyl group should preferably attack the γ^2 position. In the course of the SCS the chiral center in the α position vanishes and the chiral information is transferred to the β-carbon atom (1,2-chirality transfer, Scheme 16).



Scheme 16. Principle of 1,2-chirality transfer.

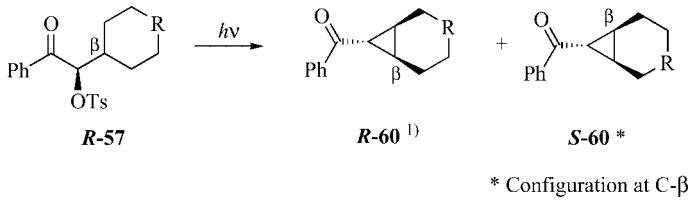
To prove our hypothesis we prepared some enantioenriched ketones (*R*)-**57** in which the R groups (Scheme 16) are all part of a saturated six-membered ring and investigated their photochemical behavior in different solvents and at different temperatures (Scheme 17, Table 2).

Table 2. Results of the irradiation of ketones (*R*)-**57**.

Product	R	Solvent	Config.[a]	*ee* [%] (*CT* [%])[b]
60f	CH(*t*Bu)[c]	DCM	(*R*)	52 (55)
60f	CH(*t*Bu)[c]	MeOH	(*R*)	45 (47)
60g	O	DCM	(*S*)	28 (31)
60g	O	MeOH	(*S*)	50 (55)
60h	N(Ts)	DCM	(*S*)	38 (38)
60h	N(Ts)	MeOH	(*S*)	48 (48)
60i	N(Boc)	DCM	(*R*)[d]	23 (25)
60i	N(Boc)	MeOH		*rac*

[a] Configuration at the β-carbon atom of the preferred enantiomer at 25 °C, assigned using VCD spectroscopy. *R*: T_0 is above 25 °C, the stereochemical reaction is enthalpy driven; *S*: T_0 is below 25 °C, the stereochemical reaction is entropy driven. [b] Chirality transfer: $CT = (ee[\mathbf{60}]/ee[\mathbf{57}]) \times 100$. [c] The *t*Bu substituent is arranged *trans* with respect to the β-carbon atom. [d] An unambiguous assignment by VCD spectroscopy was not possible.

To our delight, we observed significant chirality transfer in most cases depending on the solvent. To verify the postulated stereochemical course depicted in Scheme 16 it was necessary to determine the absolute configuration of the preferentially formed enantiomers of compounds **60f**–**i**, which was achieved in most cases by vibrational circular dichroism (VCD).[43] By this method, which is based on a comparison of experimental and calculated VCD spectra, we unambiguously determined the absolute configurations of **60f**–**h**.[33c]



Scheme 17. Stereoselective formation of bicyclic ketones **60**.

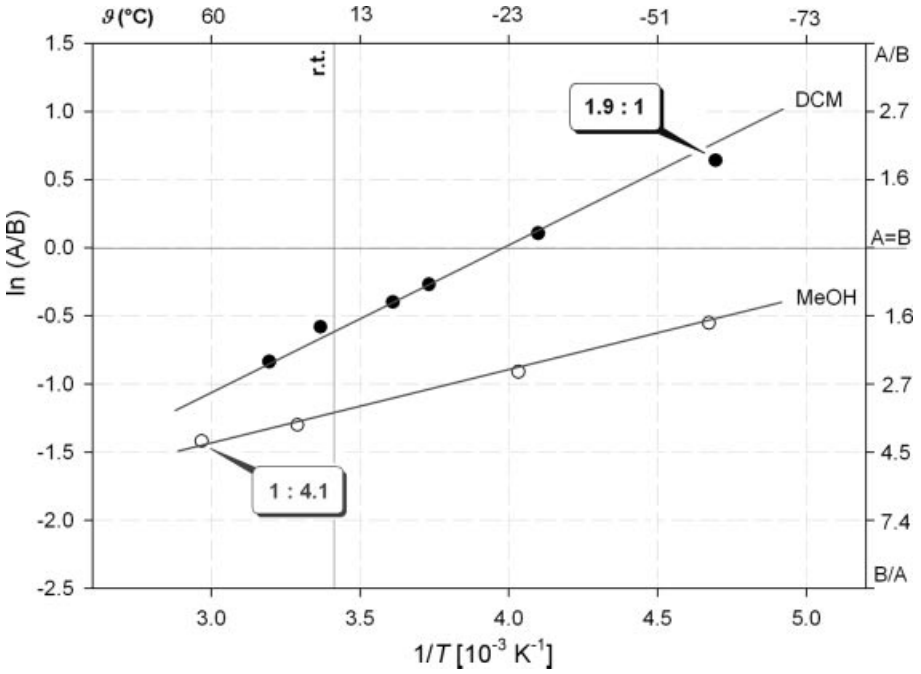


Figure 2. Temperature dependency of the stereoselective formation of **60g** (A = [(***R***)-**60g**], B = [(***S***)-**60g**]).

As a lowering of reaction temperature often leads to an increase in stereoselectivity, we carried out experiments with (*R*)-**57g** to determine the temperature dependency of stereoselectivity. The relevant Eyring plots {ln([(*R*)-**60g**]/[(*S*)-**60g**]) = $f(1/T)$} are shown in Figure 2 for the irradiation of (*R*)-**57g** in dichloromethane (DCM) and methanol (MeOH). Surprisingly, we found increasing stereoselectivity with increasing temperature in both solvents starting from room temp., as has been observed previously in other photochemical reactions.[44] This phenomenon appears if the differences in the enthalpies of activation $\Delta\Delta H^{\#}$ and entropies of activation $\Delta\Delta S^{\#}$ for the formation of the two enantiomers have the same sign. According to Equation (1), the selectivity *Se* can be calculated from the difference in free activation energies $\Delta\Delta G^{\#}$, which can be subdivided into an enthalpy and an entropy term. At a certain temperature T_0, expressed by Equation (2), these terms may compensate each other and any selectivity vanishes. Upon crossing the temperature T_0, the sign of the selectivity is reversed. The activation parameters $\Delta\Delta H^{\#}$ and $\Delta\Delta S^{\#}$, as well as T_0, obtained from the slopes of the lines in Figure 2, are summarized in Table 3.[45]

Table 3. Activation parameters for the formation of **60g**.

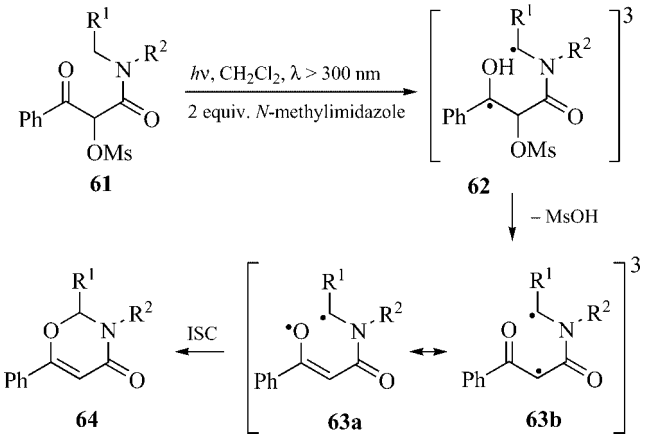
Solvent	$\Delta\Delta H^{\#}$ [kcal/mol]	$\Delta\Delta S^{\#}$ [cal/mol K]	T_0 [°C]
DCM	2.0	8.0	–23
MeOH	1.0	5.9	–104

$$Se = \ln\left(\frac{k_A}{k_B}\right) = \frac{-\Delta\Delta G^{\#}}{RT} = -\frac{\Delta\Delta H^{\#}}{RT} + \frac{\Delta\Delta S^{\#}}{R} \quad (1)$$

$$T_0 = \frac{\Delta\Delta H^{\#}}{\Delta\Delta S^{\#}} \quad (2)$$

4.2.2. Oxazinones (SCS-NY Type 2)

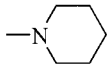
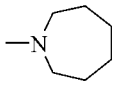
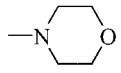
The synthesis of cyclopropanes by the SCS mechanism discussed in the preceding section corresponds to the common reaction **49**→**52a** in Scheme 14, that is, the oxoallyl radical moiety of **51** reacts as carbon-centered radical **51a**. This mode of reaction is altered if an electron-withdrawing group is directly tethered to the oxoallyl radical moiety, which is demonstrated by the photochemical reaction of α-



Scheme 18. Synthesis of oxazinones **64** by SCS.

methylsulfonyloxy-β-ketoamides **61**. These compounds are readily accessible by treating β-ketoamides with hypervalent iodine(III) reagents.[46] 1,5-Diradicals **62** are formed upon irradiation and are converted into the diradicals **63** by elimination of methanesulfonic acid. In contrast to the cyclopropane synthesis, diradicals **63** react solely as the enolate radical moiety, that is, as the oxygen radicals **63a**, to give the oxazinones **64** (Scheme 18, Table 4).[34]

Table 4. Yields of oxazinones **64**.

—N(R^1)R^2	Yield (%)
—NMe_2	44
	58
	42
	57
	64
	42

4.2.3. Indanones (SCS-NY Type 3)

The syntheses of cyclopropanes **60** and oxazinones **64** are based on reactants bearing the leaving group within the carbon chain linking the excited carbonyl group and the attacked position. If the leaving group X is positioned beyond this carbon chain, another mode of SCS is observed (cf. Scheme 14). Accordingly, if *o*-alkylaryl alkyl ketones **65** are irradiated, hydrogen abstraction from the *o*-alkyl residue takes place and the 1,4-diradicals **66** are formed (Scheme 19). These diradicals may be regarded as the triplet form of *o*-quinodimethanes and their lifetimes are considerably longer than those of nonconjugated diradicals.[47] Elimination of acid HX furnishes 1,5-diradicals **67** which cyclize, after ISC, to indanones **68**.[35a] Owing to the aforementioned longer lifetimes, this process tolerates poorer leaving groups X such as phosphates (**65h**) and even carbonates (**65i**,**j**). Therefore, this system should be suitable for novel photocleavable protecting groups[48] for phosphates and alcohols. Indeed, Klán and Wirz and their co-workers recently demonstrated that 2,5-dimethylphenacyl esters[49a–49d] and carbonates [49e] are excellent protecting groups for carboxylic acids, phosphates, sulfonates, alcohols, and phenols. The use of 2-methylphenacyl esters as photocleavable linkers in solid-phase synthesis has also been reported. [50] Note that reactants with an electron-withdrawing group at R^1 (**65e**,**f**) provide indanones **68** in good yields only if *t*BuOH is used as the solvent (condition D), whereas dihydrobenzofurans are formed as the main products in DCM (cf. section 4.2.4). The yields of selected indanones **68** are summarized in Table 5. Note that the preparation of indanones by SCS was utilized recently in the total synthesis of pterosines, a class of cytotoxic natural products occurring in bracken fern.[35b]

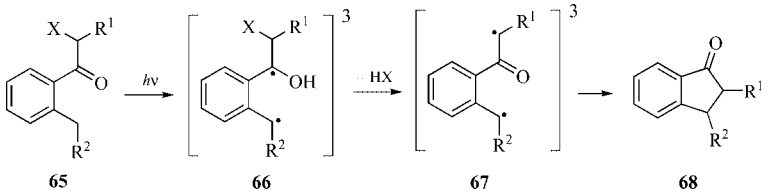
Table 5. Yields of indanones **68**.

65	R^1	R^2	X	Yield [%]	Cond.[a]
a	H	H	OMs	42	C
b	Me	H	OMs	73	C
c	Et	H	OMs	69	B
d	Ph	H	OMs	66	A
e	COOEt	H	OMs	82	D
f	$CON(CH_2)_4$	H	OMs	70	D
g	*i*Pr	H	OMs	46	A
h	Me	H	$OPO(OEt)_2$	62	A
i	Me	H	OCO*i*Bu	40	A
j	Me	H	OCOOEt	52	A
k	H	Me	OMs	42	C
l	H	COOMe	OMs	77	A
m	H	CN	OMs	58	A

[a] Conditions: A: MeOH/NMI (2 equiv.); B: MeOH; C: DCM/NMI; D: *t*BuOH.

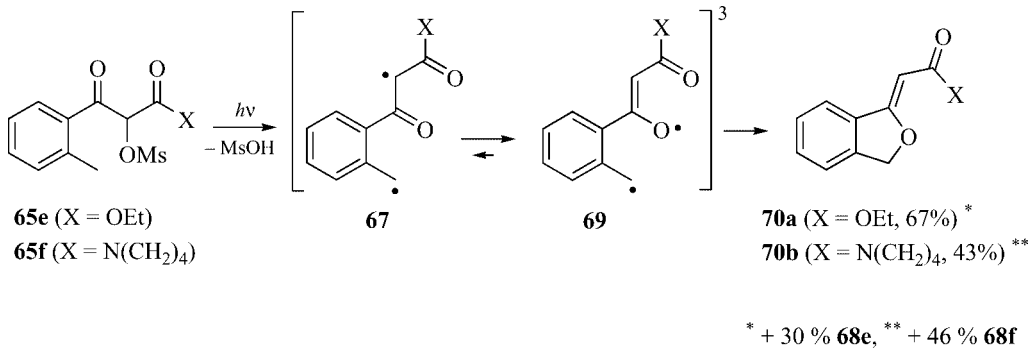
4.2.4. Dihydrobenzofurans (SCS-NY Type 4)

As discussed in section 4.2.2, the mesomeric equilibrium of the oxoallyl radical moiety depends on the electronic influence of substituents (cf. Scheme 14). Strong electron-withdrawing groups shift this equilibrium in favor of the oxygen-centered radical and cause the formation of O–C bonds instead of C–C bonds during the cyclization step. This behavior also applies to compounds **65e**,**f**, which were mentioned in the preceding section. Whereas indanones **68e**,**f** are formed if *t*BuOH is used as the solvent, the reaction outcome is fundamentally changed in dichloromethane: Now benzo[*c*]furans **70** are observed as the main products in addition to the indanones **68** (Scheme 20).[35a]



65 **66** **67** **68**

Scheme 19. Synthesis of indanones **68** by SCS.



Scheme 20. Synthesis of benzo[*c*]furans **70** by SCS.

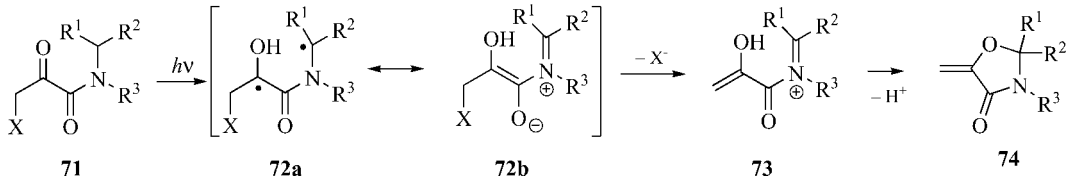
4.2.5. Related Reactions

In this section we wish to outline some reactions that are formally in accordance with the principle of the spin-center shift, but are based at best only partly on a radical mechanism. This includes the photochemical reaction of α-ketoamides **71** bearing a leaving group at the β position. These compounds react, in contrast to the previously discussed SCS reactions, predominantly from the excited singlet state. If irradiated, 1,5-hydrogen migration takes place and **72** is formed, which is better represented by an ionic (**72b**) than by a diradical structure (**72a**). After elimination of the leaving group X^-, the resulting enol **73** cyclizes to oxazolidinone **74** by an attack of the hydroxy group at the iminium carbon atom (Scheme 21). [51]

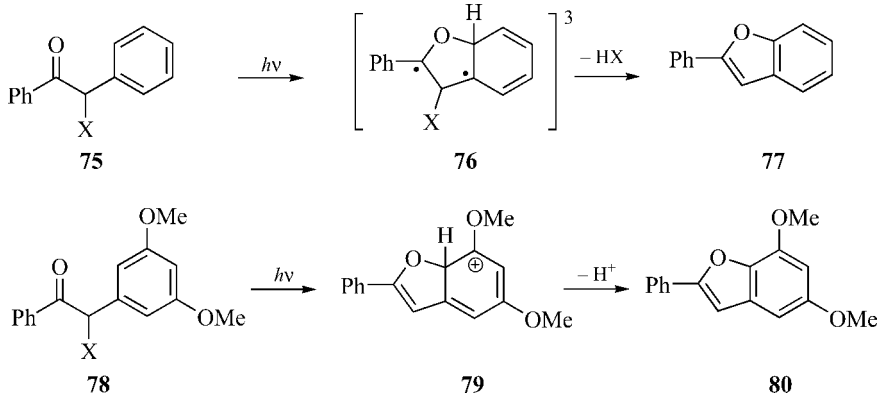
Another system that should be mentioned in this context is the photochemical cleavage of benzoin derivatives often used as photocleavable protecting groups.[48] The mechanism strongly depends on the substituents at one of the aromatic rings. Whereas the parent compounds **75** presumably react via the triplet diradicals **76**, [52] the cations **79** were assumed as intermediates if electron-donating groups are tethered to the right-hand phenyl ring. [53] In both cases, the acid HX is liberated and benzofurans are formed as the final products (Scheme 22).

5. Summary and Outlook

In this review we have shown that the concept of the spin-center shift (SCS), that is, the shift of a radical center as a result of the elimination of an acid or a leaving group, considerably extends the repertoire of radical reactions. The SCS is not a development of synthetic chemists, but was revealed to us by nature; some biochemical reaction mechanisms contain a SCS key step and the biosynthesis of deoxyribonucleotides is the most prominent example (cf. section 2). Whereas only a few applications of the SCS reaction in monoradical chemistry have been reported (section 4.1), the synthetic scope of the Norrish–Yang reaction, which proceeds via diradicals, is significantly extended by the SCS concept (section 4.2). In combination with the



Scheme 21. Photochemical reaction of α-ketoamides **71**.



Scheme 22. Photochemical cleavage of benzoin derivatives **75** and **78**.

well-investigated regioselectivity rules of the Norrish–Yang reaction, the SCS concept has allowed novel routes to cyclopropanes, indanones, oxazinones, and dihydrobenzofurans to be established. Based on a thorough understanding of the mechanism of the SCS a completely new approach to 1,2-chirality transfer could be developed.

Further mono- and diradical-mediated reactions, the scope of which could be expanded by the SCS concept, will be the subject of future research in this area.

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[17] We have estimated the pK_a value of the 2-hydroxy-2-propyl radical to be between 7 and 8. Therefore, the acidity of this radical intermediate is significantly higher than that of the corresponding alcohol (2-propanol, pK_a = 16.5). Our estimation is based on high-level ab initio calculations using the complete basis set method CBS-QB3: a) O. Muehling, Ph. D. Dissertation, Humboldt-Universität zu Berlin, **2006**, chapter 3, p. 49–50; see also: b) A. M. Toth, M. D. Liptak, D. L. Phillips, G. C. Shields, *J. Chem. Phys.* **2001**, *114*, 4595–4606; c) M. D. Liptak, G. C. Shields, *J. Am. Chem. Soc.* **2001**, *123*, 7314–7319.

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