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Stereoselective Synthesis of Cyclopropanes Based on a 1,2-Chirality Transfer

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Dedicated to Prof. Hans-Georg Henning in occasion of his 80th birthday

Abstract: A stereoselective route to enantiomerically enriched bicyclic cyclopropane derivatives **13** is described which is based on a conceptually novel 1,2-chirality transfer approach. The hyperconjugative interaction of an electronically excited carbonyl group with the σ* orbital of an adjacent C–X bond in the transition state of a hydrogen abstraction causes the preference of a certain conformation and consequently the differentiation between two diastereotopic methylene groups. The 1,2-chirality transfer is completed by a subsequent HX elimination which destroys the only stereogenic center in the reactants **12**. Furthermore, it was found that contrary enthalpic and entropic influences result in the existence of an inversion temperature T_0. Upon crossing T_0 the stereoselectivity is reversed. Considering this temperature dependency, chirality transfer efficiencies of up to 83% could be achieved. The absolute configuration of most products could be unambiguously determined by VCD spectroscopy combined with DFT calculations.

Keywords: asymmetric synthesis · chirality transfer · cyclopropanes · photochemistry · spin center shift

Introduction

In cyclization reactions between two sp^3 carbon centers the stereoselectivity of the ring closure is of particular interest because up to two new stereogenic centers can be generated. In contrast to intermolecular coupling reactions, two principles of diastereoselectivities can be distinguished:[1] The non-induced "simple" diastereoselectivity is associated with the relative arrangement of the two newly formed stereogenic centers. In the case of facial diastereoselectivity the main focus is on the relative configuration between a newly formed stereogenic center and an "old" chiral moiety localized in the substrate and controlling the stereoselectivity of the ring closure (asymmetric induction via substrate or auxiliary control).

A novel strategy for asymmetric synthesis is based on a phenomenon called "memory of chirality" or "chiral memory effect".[2] This term was introduced in 1991 by Fuji[3] and describes the conservation of the chiral information in the course of a reaction where a chiral sp^3 center is transformed into a new sp^3 center via an achiral sp^2 center in the absence of an additional permanent chiral moiety.

The Norrish–Yang cyclization,[4,5] an intramolecular C–C bond forming reaction, which results from intramolecular hydrogen abstraction by a photoexcited carbonyl compound, is an useful preparative tool to synthesize different homo- and heterocyclic compounds. Many diastereoselective examples of this photocyclization reaction are known, which can be classified according to the principles above mentioned.[6–9] Enantioselective variants of the Norrish–Yang cyclization have been successfully performed in the solid state,[10] but until quite recently no significant enantioselectivities (>10% *ee*) have been recorded for a Norrish–Yang cyclization in solution. No more than seven years ago, Bach and co-workers achieved an essential breakthrough by using chiral complexing agents capable of binding the prostereogenic Norrish–Yang substrate through hydrogen bonds.[11]

Based on the Norrish–Yang reaction, we developed the concept of spin center shift[12] which allows a completely new access to cyclopropanes.[13,14] In contrast to the classical Norrish–Yang reaction, phenyl alkyl ketones **1** with a suitable leaving group X in α-position (e.g. X = –OSO_2R) are used. At the stage of triplet 1,4-diradicals **2** the β-elimination of HX occurs faster than the "classical" Norrish–Yang reaction pathways (type II cleavage, cyclization). The result-

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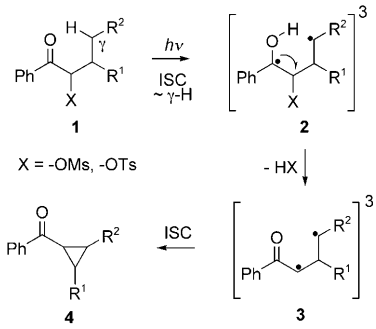
ing oxoallyl 1,3-diradicals **3** cyclize with often complete diastereoselectivity and good to excellent yields to give cyclopropanes **4** (Scheme 1).



Scheme 1. Photochemical synthesis of cyclopropanes **4**.

Herein, we report about an entirely new concept concerning the synthesis of enantiomerically enriched cyclopropanes based on a photochemically induced intramolecular 1,2-chirality transfer.[15] In the case of an asymmetric induction the chiral information is copied from a stereogenic to a prostereogenic moiety, that is, the chiral information is located both at source and destination. During a chirality transfer the prostereogenic moiety incorporates the chiral information of a stereogenic moiety which simultaneously loses this information. A distinguishing feature in the intramolecular transfer of central chirality is the distance between the source and the target of the chiral information (1,*n*-chirality transfer). The term "chirality transfer" or "transfer of chirality" is mainly associated with stereoselective reactions where the substrate loses a stereogenic center during the migration of one or more adjacent double bonds while a new stereogenic center arises elsewhere in the molecule.[16] In this context, concerted sigmatropic rearrangements are of great interest because their mostly highly ordered transition states assure an efficient generation of new stereogenic centers.[17] Consequently, relatively many examples of 1,3-chirality transfer exist but only a few examples of 1,2-chirality transfer.[18]

Results and Discussion

The concept—A simple selectivity model: By extensive quantum chemical calculations we could elucidate details of the mechanism and found that the leaving group X already has a significant impact on the first reaction step, the photochemical hydrogen shift (**1** → **2**, Scheme 1).[13] Due to hyperconjugation between the σ* orbital of the C–X bond and the π system of the excited carbonyl group, X prefers a pseudoaxial arrangement with respect to the approximately chair-like six-membered transition state (Figure 1).[13b]

If we consider enantiopure ketones of type **5** (e.g. (*R*)-**5**) with two identical substituents in β-position (Scheme 2), we can formulate two different transition states for the γ-H abstraction (**TS-A** and **TS-B**) which differ in the arrangement of the leaving group X (axial or equatorial). Based on quantum chemical calculations,[13b] **TS-A** with X in the axial position should be favored over **TS-B**. In **TS-A** the γ^1-methylene group is attacked, whereas in **TS-B** the attack takes place at the γ^2-methylene group. In other words, the carbonyl oxygen atom has to distinguish between the two diastereotopic methylene groups. During the photochemically induced hydrogen transfer and the following elimination of HX the enantiomeric diradicals **DR-A** and **DR-B** are formed, and the chiral information of the α-C atom has been transferred to the adjacent prostereogenic β-C atom (1,2-chirality transfer). Consequently, after cyclization the enantiomeric cyclopropyl ketones (*R*)-**6** and (*S*)-**6** are obtained. For given reasons the formation of (*R*)-**6** should be favored over (*S*)-**6**. Thus, during such a process a desymmetrization regarding to the methylene groups (γ^1 and γ^2) takes place.

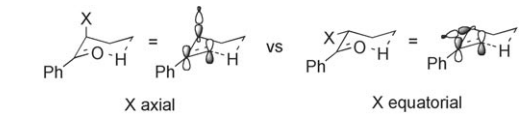
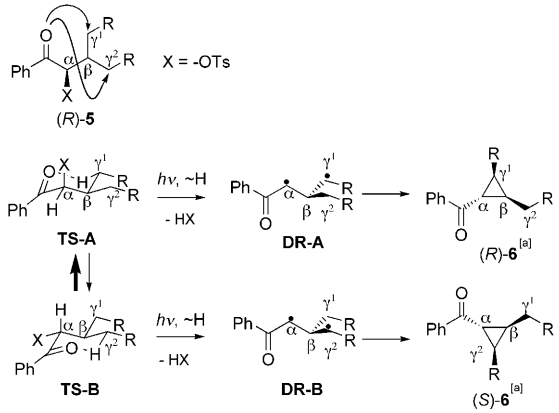


Figure 1. Axial vs equatorial arrangement of the leaving group X.

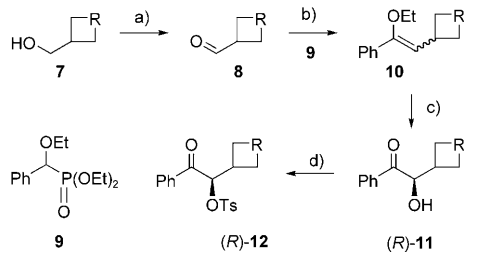


Scheme 2. The concept of 1,2-chirality transfer in the synthesis of cyclopropanes (simplified representation). [a] The configuration corresponds to C-β.

The concept shown in Scheme 2 should be applicable to all enantiopure ketones of type **5** carrying two identical substituents in β-position. It can be expected that bridging between the substituents R, in other words a conformational constraint in flexibility, creates the best situation for an efficient 1,2-chirality transfer. Therefore, we chose systems in which the atoms β, γ^1, and γ^2 (Scheme 2) are part of a five- or six-membered ring.

Synthesis of the enantiopure photochemical precursors: To verify the concept shown in Scheme 2 we first of all needed an efficient method for the synthesis of enantiopure precursors of type **5**. As sulfonates were found to be suitable leav-

ing groups (X = -OSO_2R),[13] a retrosynthetic analysis of **5** led to 2-hydroxy ketones. Various methods for the synthesis of enantiomerically enriched 2-hydroxy ketones are known. Oxidative methods starting from the ketones or their enol ethers are the most common.[19] Based on the results of Sharpless et al.[20] and Kirschning et al.,[21] we developed a very efficient sequence for the synthesis of enantiomerically enriched 2-hydroxy ketones (Scheme 3). This four-step synthesis started with alcohols **7** which were easily accessible from the corresponding carboxylic acids.[13b] Dess–Martin oxidation[22] or PCC oxidation[23] to aldehydes **8** and subsequent Horner–Wadsworth–Emmons coupling with phosphonate **9**[24] gave the enol ethers **10**. All enol ethers were isolated as *E*/*Z* mixtures (*Z* mostly predominating), a fact which had almost no effect on the stereochemical outcome of the following asymmetric dihydroxylation (AD, **10** → (*R*)-**11**). The configuration of the product is determined primarily by the choice of the ligand during the AD. In accordance with the results of Sharpless[20] application of AD-mix-α led to the *S* configured, AD-mix-β to the *R*-configured product in high enantiomeric excesses and generally unaffected by R. Because AD-mix-β[25] had yielded better results with respect to the enantiomeric excess, we chose the *R* configured 2-hydroxy ketone (*R*)-**11** as starting material of our investigations. Finally, tosylation of (*R*)-**11** with tosyl anhydride (Ts_2O) gave the photo precursors (*R*)-**12**. The results are shown in Table 1.



Scheme 3. Synthesis of the enantiopure precursors (*R*)-**12**. a) Dess–Martin periodinane (1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one) (**7a–c**,**e**,**f**) or pyridinium chlorochromate (PCC) (**7d**), dichloromethane, 0 °C → room temperature (RT). b) THF, −78 °C, *n*BuLi, + **9**, 16–24 h at RT. c) *t*BuOH/H_2O 1:1, AD-Mix-β, $MsNH_2$, 6–24 h at RT. d) Ts_2O, pyridine, cat. dimethylamino pyridine (DMAP), 0.5–6 h at RT.

Photochemical investigations: The results of the irradiation studies (25 °C, solvent: dichloromethane or methanol) are summarized in Table 2. In addition to the relative configuration of the bicylic products **13** (*exo* or *endo*), the absolute configuration at C-β of the preferred product enantiomer (*R* or *S*), and the enantiomeric excess (*ee*), a fourth stereochemical term is given: The chirality transfer (CT, [%]) which is calculated according to the equation CT = (*ee* [**13**]/*ee*[**12**])*100.[17f] The term CT is independent from the optical purity of the photochemical precursor **12** and therefore an expression for the efficiency of the 1,2-chirality transfer. From some bicyclic products **13** the absolute configuration of the excess enantiomer was determined using VCD spectroscopy.

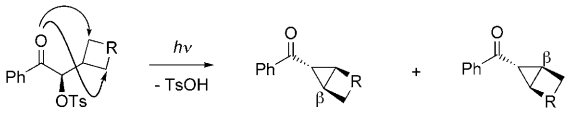
The photochemical precursors (*R*)-**12** delivered the bicyclic cyclopropyl ketones **13** in good yields and in part with considerable enantiomeric excess. With one exception [(*R*)-**12f**] the photochemical cyclization occurred with complete diastereoselectivity to the *exo* product due to an asymmetric induction of the chirality center in β position of diradicals **DR-A** and **DR-B**, respectively on the adjacent radical cen-

Table 1. Synthesis of the enantiopure photo precursors (*R*)-**12**.

Alcohol	R	Yield [%][c] **10** (*E*/*Z*)[d]	Yield [%] (*R*)-**11** (*ee* [%])[e]	Yield [%] (*R*)-**12**
7a	-CH_2-CH(*t*Bu)-CH_2-[a]	69 (25:75)	81 (95)	87
7b	-CH_2-CH(*t*Bu)-CH_2-[b]	79 (25:75)	86 (55)	87
7c	-CH_2-O-CH_2-	64 (37:63)	92 (91)	84
7d	-CH_2-N(Ts)-CH_2-	61 (53:47)	87 (99)	81
7e	-CH_2-N(Boc)-CH_2-	72 (22:78)	91 (93)	87
7f	-C_6H_4-	75 (31:69)	98 (97)	82

[a] The *t*Bu substituent is *trans* with respect to C-β. [b] The *t*Bu substituent is *cis* with respect to C-β. [c] Yield over two steps (**7** → **8** → **10**). [d] The *E*/*Z* ratio was determined by ^{1}H NMR. [e] The enantiomeric excess (*ee*) was determined by HPLC (Chiralcel-OD, Chiralpak-AD-H).

Table 2. Results of irradiation at 25 °C.



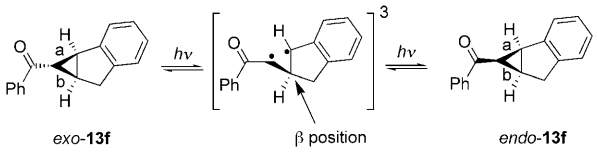
(*R*)-**12** *exo*-(*R*)-**13** *exo*-(*S*)-**13**

(*R*)-**12** (*ee* [%])	Solvent[a]	Yield **13** [%][b]	Rel. conf. **13**	C-β conf. **13**[c]	*ee* [%][f] (CT [%])[g]
a (95)	CH_2Cl_2	79	*exo*	*R*	52 (55)
a (95)	MeOH	n.d.	*exo*	*R*	45 (47)
b (55)	CH_2Cl_2	72	*exo*	n.d.[d]	10 (18)
c (91)	CH_2Cl_2	74	*exo*	*S*	28 (31)
c (91)	MeOH	n.d.	*exo*	*S*	50 (55)
d (99)	CH_2Cl_2	78	*exo*	*S*	38 (38)
d (99)	MeOH	n.d.	*exo*	*S*	48 (48)
e (93)	CH_2Cl_2	69	*exo*	*R*[e]	23 (25)
e (93)	MeOH	n.d.	*exo*	–	rac.
f (97)	CH_2Cl_2	78	80 % *exo* 20 % *endo*	n.d.[d]	49 (51)

[a] Irradiation at 25 °C in dichloromethane in the presence of *N*-methylimidazole as acid scavenger or in methanol without acid scavenger. For details see ref. [13b]. [b] Yield after conversion of the racemic precursors **12a**,**c–f**. For details see ref. [13b]. Irradiations in MeOH were not performed on a preparative scale. Therefore, the yield in MeOH was not determined. [c] C-β Configuration of the excess enantiomer at 25 °C, assigned by VCD spectroscopy. [d] Not determined. [e] A complete assignment with VCD spectroscopy was not possible. [f] The enantiomeric excess (*ee*) was determined by HPLC (Chiralcel-OD, Chiralpak-AD-H). [g] Chirality transfer according to ref. [17f]: CT = (*ee* [**13**]/*ee* [**12**]) × 100.

ters (Scheme 2).[13] Thus, the stereoselectivity obtained in the formation of **13** exclusively reflects the efficiency of the 1,2-chirality transfer.

Compound **13f** contains a π-electronic system in conjugation with the cyclopropyl moiety. It is well known that upon irradiation benzoyl cyclopropanes of such type undergo an efficient *cis*/*trans*- and *exo*/*endo*-photoisomerization, respectively, until a photostationary state is reached.[26] This isomerization proceeds with no loss of the chirality information in β position because after photochemical excitation bond a) is cleaved exclusively (Scheme 4).



Scheme 4. *exo*/*endo* Photoisomerization of **13f** with no loss of the chirality information in β position.

The selectivity model depicted in Scheme 2 predicts the preferred formation of (*R*)-**13** from (*R*)-**12**. However, no consistent picture emerges from our irradiation studies at 25 °C (Table 2): Irradiation of (*R*)-**12a** delivers predominantly the expected *R*-configured *exo*-**13a**, whereas from (*R*)-**12c** and (*R*)-**12d** the product enantiomer with *S* configuration at C-β is mainly generated. To clarify this contradiction, systematic examinations were carried out to investigate the effect of temperature on the stereoselectivity.

The roles of enthalpy and entropy on stereoselectivity: For the first time, Scharf investigated in detail the temperature dependence of the selectivity of photochemical processes by means of the Paterno–Büchi reaction.[27] He found that the reaction temperature has no uniform influence on the stereoselectivity of the product formation. In contrast to the prevalent opinion—the lower the reaction temperature, the higher the stereoselectivity—a constant behavior or even a decrease can also be observed. This appears contra-intuitive at first but can be easily explained bearing in mind the rules for temperature-dependent selectivity processes.

In a kinetically controlled unimolecular reaction leading to two enantiomers **A** and **B**, the selectivity S is expressed by $S = \ln(k_A/k_B)$ where k_A and k_B are the overall rate constants for the formation of **A** and **B**, respectively. Then, the temperature dependence of the stereoselectivity for the two reaction channels can be analyzed according to the Eyring formalism[28] $S = \ln(k_A/k_B) = -\Delta\Delta G^{\neq}/RT$. Thus, the preferred formation of one enantiomer (**A** or **B**) is based on the difference between the free activation energies $\Delta\Delta G^{\neq}$ of both reaction paths which in turn consists of an enthalpic and an entropic term ($\Delta\Delta G^{\neq} = \Delta\Delta H^{\neq} - T\Delta\Delta S^{\neq}$, Gibbs–Helmholtz equation): $S = \ln(k_A/k_B) = -\Delta\Delta H^{\neq}/RT + \Delta\Delta S^{\neq}/R$. A special situation arises if enthalpy and entropy promote the formation of opposite enantiomers leading to an inversion of selectivity by temperature. In this case, we obtain an excess of one enantiomer at low temperature and of the other one at high temperature. Figure 2 schematically

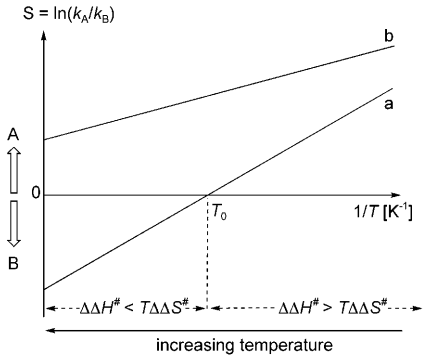
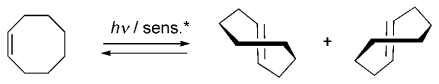


Figure 2. Eyring Plots a) with and b) without selectivity reversal at T_0 (according to ref. [29b]).

shows the corresponding linear Eyring plots. Plot a crosses the *x* axis ($S = \Delta\Delta G^{\neq} = 0$) at a special temperature $T_0 = \Delta\Delta H^{\neq}/\Delta\Delta S^{\neq}$[29] where enantiomers **A** and **B** are formed as a racemic mixture. Since the absolute temperature is always greater than zero, an inversion of product configuration can only be observed if $\Delta\Delta H^{\neq}$ and $\Delta\Delta S^{\neq}$ have the same sign. Otherwise, enthalpy and entropy play in favor of the same enantiomer (e.g. **A**, plot b, Figure 2) and a reversal of selectivity by variation of the temperature cannot occur. At T_0 the enthalpic and entropic contributions compensate each other ($\Delta\Delta H^{\neq} = T\Delta\Delta S^{\neq}$) affording no stereodifferentiation. Below T_0 the enthalpy difference $\Delta\Delta H^{\neq}$ controls the selectivity process ($\Delta\Delta H^{\neq} > T\Delta\Delta S^{\neq}$), while the entropic term $T\Delta\Delta S^{\neq}$ is dominant at temperatures higher than T_0 ($\Delta\Delta H^{\neq} < T\Delta\Delta S^{\neq}$).

A couple of thermal[30] and photochemical[31] reactions accompanied by a reversal of selectivity at T_0 are reported in literature.[32] One of the best investigated photochemical reactions of this type is the enantiodifferentiating *Z*/*E* photoisomerization of (*Z*)-cyclooctene in the presence of a chiral sensitizer (Scheme 5). By variation of temperature,[33] pressure[34] or solvent[35] it is possible to control which *E* enantiomer is formed preferentially.[36]



Scheme 5. Enantiodifferentiating *Z*/*E* photoisomerization of cyclooctene.

By means of (*R*)-**12a**,**c**–**e** the effect of temperature (and solvent) on the stereoselectivity of the reaction (*R*)-**12** → **13** was investigated in detail. The corresponding Eyring plots are given in Figure 3. The activation parameters calculated from the Eyring plots are summarized in Table 3.

With one exception (Table 3, entry 2) $\Delta\Delta H^{\neq}$ and $\Delta\Delta S^{\neq}$ have the same sign leading to a temperature T_0 where the

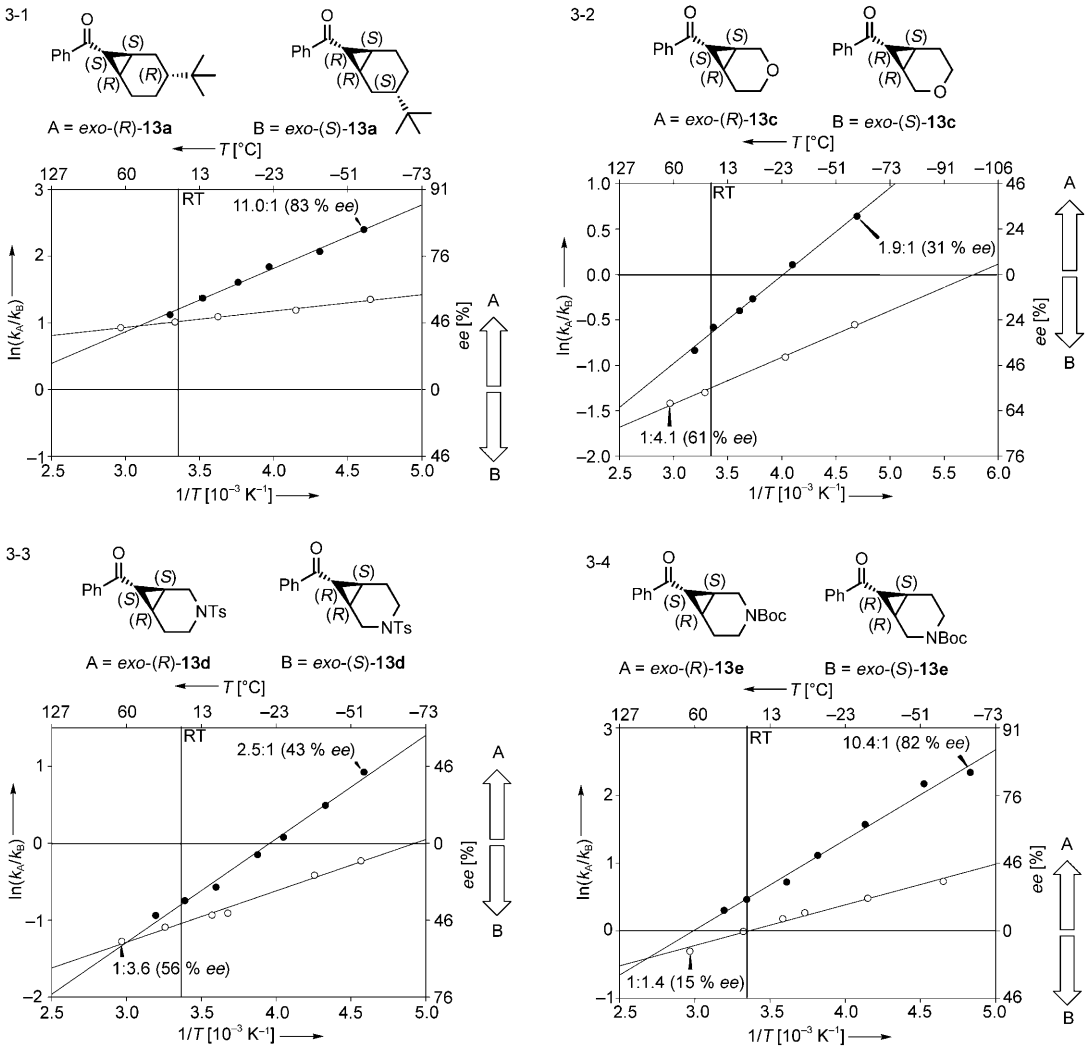


Figure 3. Eyring plots of (*R*)-**12** → *exo*-**13**: ● = CH_2Cl_2, ○ = MeOH.

respective photo product *exo*-**13** results as a racemic mixture. In four of eight cases (Table 3, entries 3–6) T_0 lies below room temperature and at 25 °C the *S* enantiomer is formed preferentially due to entropy control (positive $\Delta\Delta G^{\neq}$ values). In contrast, photolysis of (*R*)-**12a** always gives the enthalpic-favored *exo*-(*R*)-**13a** in excess (negative $\Delta\Delta G^{\neq}$ values) and independently of the used solvent because T_0 either is far above the boiling point of the solvent (dichloromethane) or does not exist (methanol). For similar reasons, irradiation of (*R*)-**12e** in dichloromethane yields predominantly the *R* enantiomer within the investigated temperature range. However, in methanol selectivity reversal occurs near room temperature (T_0 = 25 ± 3 °C) and *exo*-**13e** is formed as racemic mixture.

Moreover, the solvent has a uniform influence on the stereochemical outcome of the investigated reactions. A change of the solvent from dichloromethane to methanol causes a decrease of the difference of $\Delta H^{\neq}$ and $\Delta S^{\neq}$ (absolute values) between both reaction channels and a shift of T_0 to lower temperatures [(*R*)-**12c–e**]. In the case of (*R*)-**12a** photolysis in methanol induces a change of sign in

Table 3. Activation parameters ($\Delta\Delta H^{\neq}$, $\Delta\Delta S^{\neq}$, $\Delta\Delta G^{\neq}$, T_0) calculated from the Eyring plots.

Entry	**12**	Solvent[a]	$\Delta\Delta H^{\neq}$ [b]	$\Delta\Delta S^{\neq}$ [c]	$\Delta\Delta G^{\neq}$ [d]	C-β conf. *exo*-**13**[e]	T_0 [°C]
1	**a**	CH_2Cl_2	−1.89 ± 0.08	−3.94 ± 0.28	−0.72 ± 0.08	*R*	207 ± 18
2		MeOH	−0.49 ± 0.03	0.40 ± 0.10	−0.60 ± 0.03	*R*	–
3	**c**	CH_2Cl_2	−1.92 ± 0.06	−7.71 ± 0.23	0.38 ± 0.06	*S*	−24 ± 2
4		MeOH	−1.02 ± 0.05	−5.89 ± 0.16	0.74 ± 0.05	*S*	−100 ± 6
5	**d**	CH_2Cl_2	−2.67 ± 0.12	−10.58 ± 0.45	0.48 ± 0.12	*S*	−20 ± 2
6		MeOH	−1.33 ± 0.08	−6.53 ± 0.27	0.62 ± 0.08	*S*	−70 ± 6
7	**e**	CH_2Cl_2	−2.64 ± 0.13	−7.90 ± 0.50	−0.29 ± 0.13	(*R*)[f]	61 ± 5
8		MeOH	−1.19 ± 0.08	−4.01 ± 0.29	0.00 ± 0.08	rac.	25 ± 3

[a] Irradiation at 25 °C in dichloromethane in the presence of *N*-methylimidazole as acid scavenger or in methanol without acid scavenger. [b] kcal mol^{-1}. [c] cal mol^{-1} K^{-1}. [d] 25 °C, kcal mol^{-1}. [e] C-β configuration of the excess enantiomer at 25 °C, assigned by VCD spectroscopy. [f] A complete assignment with VCD spectroscopy was not possible.

$\Delta\Delta S^{\ddagger}$. Consequentially, enthalpy and entropy play in favor of the same enantiomer and a reversal of selectivity cannot occur.

Determination of the absolute configuration via VCD spectroscopy: A couple of methods has been developed over the years to determine the absolute configuration in chiral molecules, for example, anomalous X-ray scattering,[37] different chiroptical methods (electronic circular dichroism [CD],[38] vibrational circular dichroism (VCD),[39] optical rotation dispersion [ORD][40]) and nuclear resonance spectroscopy (NMR) in combination with chiral derivatizing agents (CDAs).[41]

Particularly predestined for conformationally rigid molecules of type **13** is vibrational circular dichroism (VCD).[39] VCD is the extension of electronic CD[38] into (near-)infrared regions of the spectrum, namely the difference in the IR absorption between left and right circularly polarized radiation during a vibrational transition. Only chiral molecules can display this difference. Pairs of enantiomers have VCD spectra of identical magnitude but opposite sign at all frequencies. Analogous to the comparison of UV/Vis and IR spectra, VCD spectra are much richer in spectral features than electronic CD spectra. The widths of vibrational transitions are much narrower leading to more highly resolved spectra.

VCD studies for absolute configuration determination consist of a combination of spectral measurement and quantum mechanical calculations. In this context, it is highly advisable to calculate both IR and VCD spectrum. Only a good agreement between observed and calculated IR spectrum allows a comparison of the respective VCD spectra. For IR/VCD calculations the best compromise between accuracy and computational cost is currently offered by using density functional theory (DFT) with a hybrid functional like B3LYP or B3PW91 and a 6-31G* basis set as a minimum. All IR/VCD calculations were carried out at the DFT level with the Gaussian 98 program package[42] using the hybrid functional B3LYP[43] and the 6-31G* basis set. Based on the optimized geometries, single point calculations were accomplished with the same DFT method and a higher 6-311++G** basis set. For comparison with experimental spectra, the calculated frequencies were uniformly scaled with the factor 0.9614 and the IR and VCD intensities were represented as Pseudo-Voigt bands with 8 cm^{-1} half width. The calculation has been started with the selection of a specific absolute configuration of the particular photo product *exo*-**13** followed by an analysis of the conformational flexibility to determine which conformers are significantly populated under the experimental measurement conditions. Here, it was advantageous that the bicyclic products *exo*-**13** are comparatively rigid molecules and so only few conformers have to be taken into account. Afterwards, the exact relative energies of the remaining low-energy conformers were determined to calculate the IR/VCD spectrum as a linear combination of the computed spectral data.

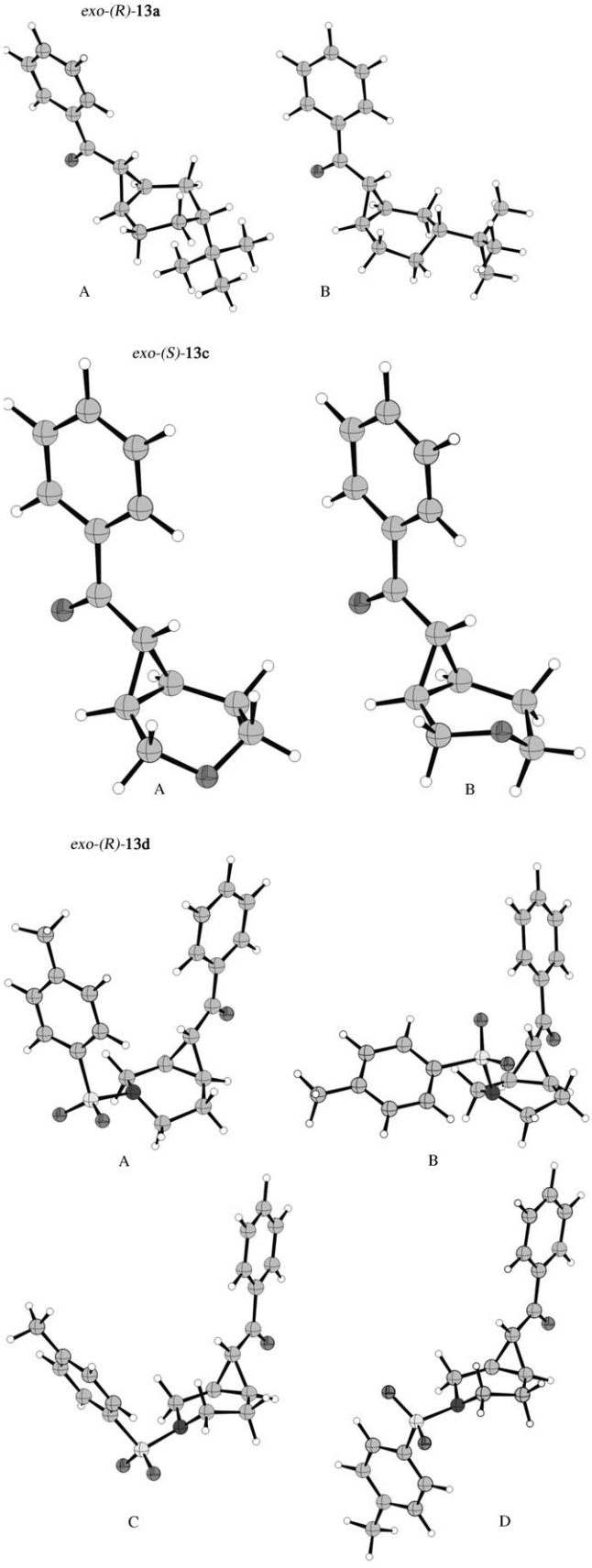


Figure 4. Optimized geometries (B3LYP/6-311++G**//B3LYP/6-31G*).

In close collaboration with Bruker Optics (Ettlingen, Germany) we succeeded in unambiguously determining the absolute configuration of *exo*-**13a**,**c**,**d**. The optimized geometries (B3LYP/6-311++G**//B3LYP/6-31G*) of all relevant conformers are given in Figure 4. The resulting relative energies and fractional Boltzmann populations are summarized in Table 4. The experimental and calculated IR and VCD spectra, respectively, are shown in Figure 5.

Table 4. Relative energies and fractional Boltzmann populations for conformers of *exo*-**13a**,**c**,**d** (B3LYP/6-311++G**//B3LYP/6-31G*).

Conformer	E_{rel} [kcal mol^{-1}]	P(25 °C) [%]
exo-(*R*)-**13a-A**	1.9	3.9
exo-(*R*)-**13a-B**	0.0	96.1
exo-(*S*)-**13c-A**	3.9	0.1
exo-(*S*)-**13c-B**	0.0	99.9
exo-(*S*)-**13d-A**	0.2	36.0
exo-(*S*)-**13d-B**	0.0	50.5
exo-(*S*)-**13d-C**	1.3	5.6
exo-(*S*)-**13d-D**	1.1	7.9

The approach is illustrated firstly by means of compound *exo*-**13c**. A conformational analysis of the enantiomer *exo*-(*S*)-**13c** showed that the benzoyl group adopts a nearly bisected conformation with respect to the cyclopropane ring due to a stereoelectronic interaction between the carbonyl moiety and the cyclopropane ring.[44] In terms of the tetrahydropyrane ring two half-chair conformations[45] (*exo*-(*S*)-**13c-A** and *exo*-(*S*)-**13c-B**) have to be distinguished. In consequence of a 1,4-transannular interaction conformer **A** is 1.9 kcal mol^{-1} less favored compared with **B**. This correlates with a fractional Boltzmann population of P_A(25 °C) = 3.9 % under IR/VCD measurement conditions. Thus, conformer **A** will not contribute significantly to the IR/VCD spectrum and has not to be considered. This conclusion was impressively confirmed by a very good agreement with the experimental IR and VCD spectra, respectively (Figure 5). The VCD study thus established the configuration of the excess enantiomer of *exo*-**13c** as (1*R*,6*S*,7*R*) (~*exo*-(*S*)-**13c**).

For *exo*-**13a** only one of two ring conformers has to be taken into account as well. The *tert*-butyl moiety in 3-position acts as a conformational anchor and a pseudo equatorial arrangement (**B**) is highly favored (ΔE_{rel} = 3.9 kcal mol^{-1}, P_A(25 °C) = 0.1 %, P_B(25 °C) = 99.9 %). As a result, the IR/VCD calculation of *exo*-(*R*)-**13a-B** (1*R*,3*R*,6*R*,7*S*) gave a very good correlation with the corresponding experimental spectra.

The IR/VCD calculations of the 3-azabicyclo-[4.1.0]heptanes *exo*-**13d**,**e** turned out to be slightly more complicated. In both cases four conformers (**A**–**D**) were found because an additional degree of freedom, namely the *N*-substituent (Ts or Boc), is involved. However, the respective conformers **C** and **D** are at least 1.0 kcal mol^{-1} higher than the corresponding lowest energy conformation. Consequently, conformers **C** and **D** were not considered because only a small contribution to the IR/VCD spectra was expected. Conformer **A** can be transformed into **B** by rotation around the N,S- and N,C(=O)-bond, respectively. In rotamer *exo*-(*S*)-**13d-A** the *p*-tolyl group of the angular tosyl moiety is sticking out into the *endo* half space of the bicyclus. Therefore, **A** is around 0.2 kcal mol^{-1} less favored than **B**

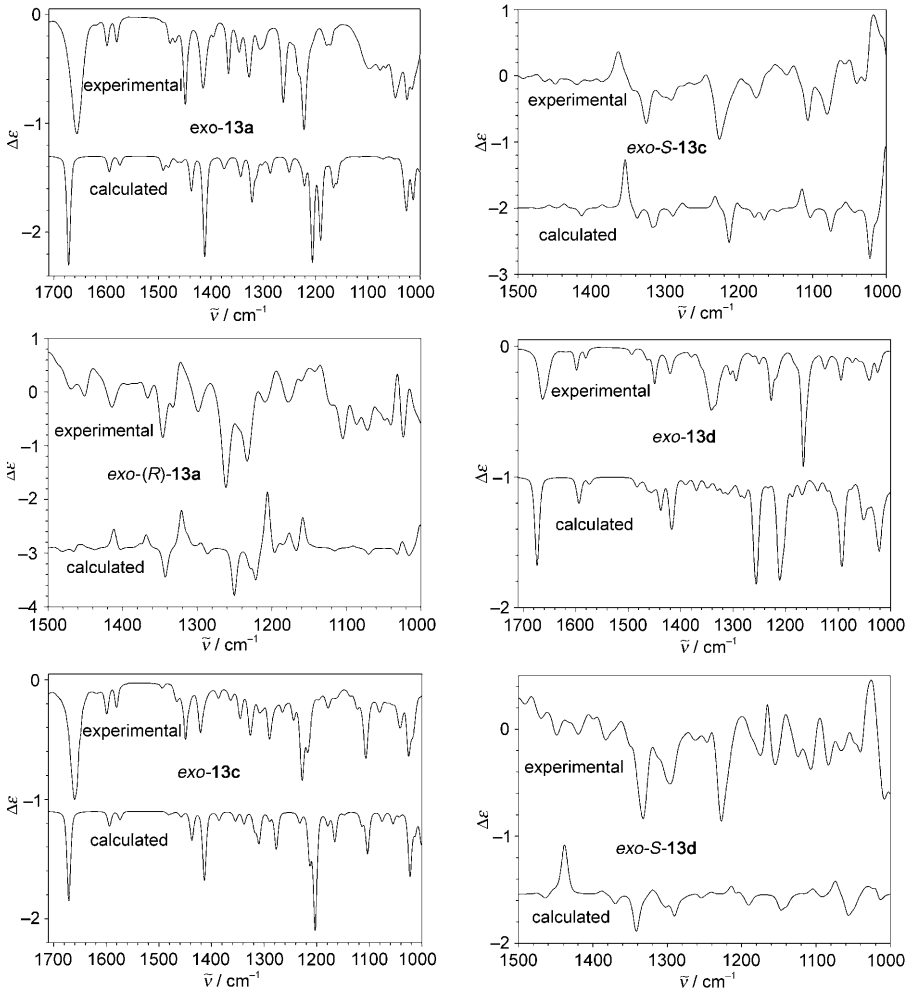


Figure 5. Comparison of experimental and calculated IR and VCD spectra.

corresponding to fractional Boltzmann populations of P_A-(25 °C) = 42 % and P_B(25 °C) = 58 %. The resulting composite spectra *exo*-(*S*)-**13d-A** and *exo*-(*S*)-**13d-B** are in quite good agreement with the experimental data. Thus, the VCD analysis identified the configuration of the excess enantiomer of *exo*-**13d** as (1*R*,6*S*,7*R*) (~*exo*-(*S*)-**13d**).

However, in *exo*-**13e** the analogous conformers **A** and **B** are of nearly equal energy. The hybrid spectra of 54 % **A** and 46 % **B** have shown an inadequate correlation with the observed spectra, and so no conclusion about the absolute configuration of *exo*-**13e** could be made (see Supporting Information).

Conclusion

In summary, we reported on a completely novel concept of stereoselectivity based on a 1,2-chirality transfer. In the initial step of a photochemical cyclopropane synthesis,[13] which is a special application of the concept of spin center shift,[12] an electronically excited carbonyl group can interact with a σ* orbital of an adjacent C–X bond causing a preferred geometry of the corresponding cyclohexane-like transition state for the hydrogen abstraction (Scheme 2). In the consequence of this interaction, the carbonyl group can distinguish between two diastereotopic methylene groups in γ position. Because the initial chirality information is destroyed in the next step by elimination of acid HX, an 1,2-chirality transfer takes place. To our surprise, we found after careful determination of the absolute configuration of the resulting bicyclic cyclopropane derivatives **13** by VCD spectroscopy that the stereochemical outcome of the reaction is not uniformly for different derivatives. An extensive investigation of the temperature dependence of the stereoselectivity revealed that contrary enthalpic and entropic contributions are responsible for this unexpected behavior. In most cases, we could determine a temperature T_0[29] at which these contributions compensate each other and the stereoselectivity vanishes. With these findings in hand we could obtain the products **13** with partly impressive stereoselectivities by proper choice of the irradiation temperature (e.g. *ee* 83 % for **13a** at −56 °C). We hope that our results will inspire further interesting stereoselective photochemical as well as thermal reactions.

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