

RESEARCH ARTICLE

Stereoelectronic effects: Perlin effects in cyclohexane-derived compounds

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Abstract

Stereoelectronic effects in cyclohexanones, methylenecyclohexanes, spiro, and epoxy compounds of cyclohexanes and further derivatives were investigated by measuring $^1J_{C,H}$ coupling constants and by identification of Perlin effects, that is, of differences in the coupling constants for equatorial and axial C—H bonds in the methylene groups of six-membered rings. The Perlin effects were correlated with results from natural bond orbital analyses. NMR experiments and calculations were performed with conformationally restricted 4-*tert*-butyl-substituted derivatives. It turned out that the coupling constants are strongly influenced not only by stereoelectronic interactions with C=C, C=O, and C=N π bonds, or with the π -type C—C or C—O bonds of the three-membered rings, but also by the s character of the respective C—H bonds' carbon orbital. Reliable correlations of measured and calculated coupling constants were achieved with B3LYP/6-311++G(d,p) and BP86/aug-cc-pVTZ-J functionals.

KEYWORDS

coupling constants, cyclohexane derivatives, DFT calculations, NBO analysis, spiro compounds, stereoelectronic effects

1 | INTRODUCTION

Stereoelectronic effects have a significant influence on the stability, structure, and reactivity of chemical compounds and on their physical and spectroscopic properties.^[1] A profound knowledge of these effects allows for a better understanding and prediction of these features. In the course of our research in the field of stereoelectronic effects, especially of those in sulfur compounds,^[2] we recently investigated thianes and oxidized substrates thereof.^[3] Here, we considered it useful to compare the then obtained data with those of cyclohexanones and of further cyclohexane derivatives. Nevertheless, because

we realized that most of the desired data had not been investigated or published, we decided to collect these in a discrete project.

It has already been mentioned by Perlin and Casu that those equatorial hydrogens in tetrahydropyranes (actually in carbohydrates), which are next to the ring oxygen, show a larger $^1J_{C,H}$ coupling than the respective axial hydrogens.^[4] This effect, which was later called the normal Perlin effect, can be traced back to an $n_O \rightarrow \sigma^*_{C,Hax}$ interaction weakening the axial C—H bond.^[5] A so-called reversed Perlin effect has later been observed in 1,3-dithianes. At position C-2 (between the two sulfur atoms), the $^1J_{C,Hax}$ coupling is larger than the

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$^1J_{C,Heq}$ coupling. This was explained by the rather poor donor ability of the lone pairs at the sulfur atoms; the stereoelectronic effects of these are overcompensated by strong $\sigma_{C,S} \rightarrow \sigma_{C,Heq}^*$ and $\sigma_{C,Heq} \rightarrow \sigma_{S,C}^*$ interactions.^[2c,6] Stereoelectronic interactions in cyclohexanones^[7] and the resultant Perlin effects^[8] have intensely been studied, because these seem to have a significant influence on the stereoselectivity of cyclohexanone reactions, especially in nucleophilic attacks to the carbonyl group.^[9] Experimental investigations of these effects are preferentially performed with conformationally constrained substrates to unambiguously differentiate the two faces of the carbonyl group. 4-*tert*-Butyl-substituted cyclohexanones are mostly used in this context, because this bulky substituent prefers an equatorial position and thus leads to an unambiguous fixation of the conformation.^[10] On the other hand, it is located far enough from the reaction center and has no significant influence on the stereochemistry of the investigated reactions nor on the bond properties of bonds around the carbonyl group.

It has been argued for nucleophilic attacks in cyclohexanones that the axial hydrogen atoms at positions C-2 and C-6 interact with the C=O bond in a $\sigma_{C,Hax} \rightarrow \pi_{C=O}$ interaction, which leads to a weakening of the axial C–H bonds and of the π bond (double bond/no bond resonance,^[1a,11] Figure 1a), to a rehybridization of the carbonyl's carbon atom (to facilitate and increase this interaction), and thus to a pyramidalization (Figure 1b). The augmented lobe of the carbon's p orbital leads to a preferred attack of a nucleophile from the top face of the molecule, at least for small nucleophiles, which are not hindered by the axial hydrogen atoms at carbons C-3 and C-5.^[9] Nevertheless, alternative explanations have been given for the observed selectivities.^[12]

The $\sigma_{C,Hax} \rightarrow \pi_{C=O}$ interaction or double bond/no bond resonance reduces the bond order of the respective axial C–H bonds and can thus not only be quantified by quantum chemical methods but can further be estimated by measuring the $^1J_{C,H}$ coupling constants. A

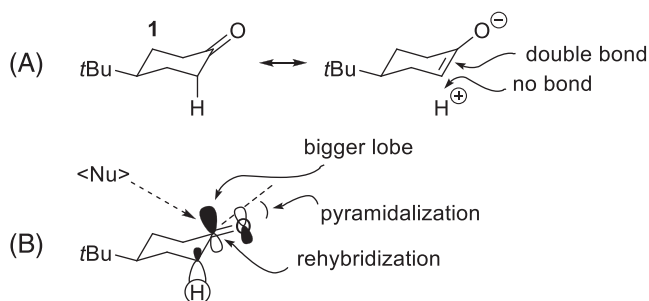


FIGURE 1 (a) Double bond/no bond resonance in cyclohexanones and (b) $\sigma_{C,Hax} \rightarrow \pi_{C=O}$ interaction leads to rehybridization and pyramidalization of the carbonyl carbon. Nucleophilic attack from the top is preferred for small nucleophiles

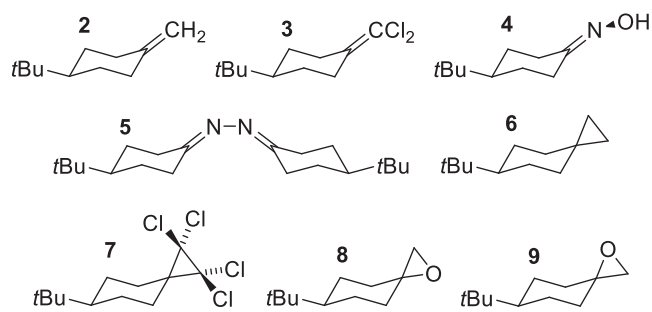


CHART 1 Investigated derivatives of cyclohexane

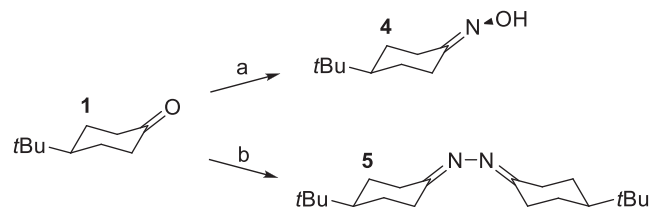
decreased bond order should result in smaller coupling constants.^[13]

Herein we report on the synthesis of cyclohexane derivatives **1–9** (Chart 1), on the determination of $^1J_{C,H}$ coupling constants in these compounds, and on their correlation with stereoelectronic effects, calculated by quantum chemical methods. We used conformationally constrained 4-*tert*-butyl-substituted substrates in all spectroscopic investigations to allow for the unambiguous differentiation of the axial and the equatorial hydrogen atoms. These substituted molecules were similarly used for the quantum chemical calculations.

2 | SYNTHESIS OF CYCLOHEXANE-DERIVED COMPOUNDS

Oxime **4**^[14] and an analogous hydrazone were synthesized with standard protocols starting with commercially available 4-*tert*-butylcyclohexanone (**1**). Reaction of **1** with hydrazine hydrate did not furnish the expected simple cyclohexylidenehydrazine but a 1,2-dicyclohexylidenehydrazine **5**,^[15] which we considered similarly suitable for the intended investigations (Scheme 1).

Wittig olefination^[16] of cyclohexanone **1** yielded methylenecyclohexane **2** with 46% yield, and dichloromethylation^[17] as the first step of a Corey–Fuchs reaction gave access to a dichloroalkene **3** (96%).



SCHEME 1 Synthesis of oxime **4** and hydrazone **5**. Conditions: (a) $H_2NOH \cdot HCl$, $NaOH$, grinding, rt, 50 min (27% [89%–96%^[14]]) and (b) $H_2NNH_2 \cdot H_2O$, $MeOH$, $0^\circ C \rightarrow 60^\circ C$, 1 h (38%)

These alkenes could be reacted with in situ-generated dichlorocarbene^[18] to yield the respective spiro compounds **7** and **10**. A comparison of measured and calculated spectra suggested that the major isomer of dichloro compound **10** should bear the chlorinated carbon in pseudo-axial orientation. However, reduction of **10** with lithium in liquid ammonia^[19] led to the parent substrate **6**, whose isolation turned out to be quite tedious. Its volatility prevented an immediate isolation. It was thus purified by preparative thin-layer chromatography (TLC) with pentane as mobile phase. Deuterated chloroform (CDCl₃) was used as eluent and residual pentane was removed as azeotrope with CDCl₃ to yield the product as a solution suitable for NMR spectroscopic investigations (Scheme 2).

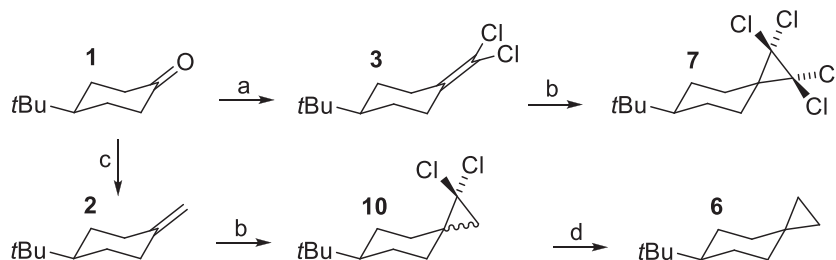
A practical synthesis of epoxides **8** and **9** has already been described by Franssen and coworkers.^[20] Although the preparation of these compounds is either achieved starting with cyclohexanone **1** using a Corey–Chaykovsky reaction or by epoxidation of alkene **2** with *meta*-chloroperbenzoic acid (mcpba), their separation had turned out to be not possible with conventional methods. It has therefore been proposed to react the mixture of epoxides with a bromide source (bromodimethylsulfonium bromide^[21]) to obtain the respective bromohydrins **11** and **12** again as a mixture of isomers. These isomers could now be separated and reacted with sodium hydroxide as base to obtain epoxides **8** and **9** in isomerically pure form. Starting with cyclohexanone **1**, we obtained epoxides **8** and **9** over three steps in total yields of 6% and 9%, respectively (Scheme 3).

3 | DETERMINATION OF ¹J_{C,H} COUPLING CONSTANTS

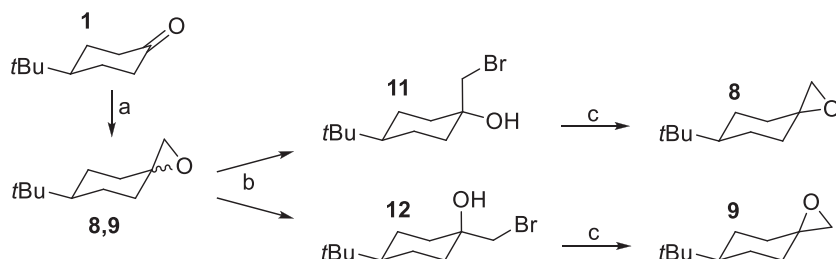
¹J_{C,H} coupling constants of the cyclohexane-derived compounds **1–9** were determined; the experimental data are here ordered in two sets for the compounds **1–5** containing double bonds (Figure 2, left section) and for the spiro compounds **6–9** (right section). ¹J_{C,H} coupling constants are given as green data points with error bars for every distinguishable C–H bond of the six-membered rings. Perlin effects for methylene groups are given as vertical blue bars, where the upward bars indicate normal Perlin effects (¹J_{C,Heq}–¹J_{C,Hax} > 0). Reversed Perlin effect (¹J_{C,Heq}–¹J_{C,Hax} < 0) were not observed for these compounds. Numeric values for all measured coupling constants and Perlin effects are given in the supporting information. Oxime **4** and hydrazone **5** show different values for carbon atoms C-2 and C-6 and for C-3 and C-5, respectively, because the lifetime of the C=N bonds' configurations is longer than the NMR time scale. Hydrazone **5** is present as a ~1:1 mixture of two rotamers, which showed slightly differing ¹³C shift and coupling constants. The small shift differences and the close to 1:1 mixture prevented an assignment of the signals to the respective rotamer. Consequently, we give average values for the coupling constants in the figure, where the respective measured values are specified in the supporting information.

Significant (normal) Perlin effects are observed for the α positions of the cyclohexanone derivatives **1–5**, that is, the ¹J coupling constants of equatorial C–H bonds are

SCHEME 2 Synthesis of alkenes **2** and **3** and of spiro compounds **6** and **7**. Condition: (a) CCl₄, PPh₃, MeCN, 0°C → rt, 75 min (96%); (b) CHCl₃, NaOH, cat. Me(CH₂)₁₅NMe₃Br, H₂O, rt, 21 h (**7**: 35%; **10**: 57%); (c) Ph₃PMeBr, BuLi, Et₂O, rt, 35 min (46%); and (d) Li, NH₃ (l) (**6** is obtained as solution in CDCl₃)



SCHEME 3 Synthesis of epoxides **8** and **9**. Conditions: (a) Me₃SI, KO^tBu, DMSO, rt, 21 h; (b) BrSMe₂Br; MeCN, rt, 20 min; separation of isomers (**11**: 8%, two steps [9%^[20]]; **12**: 10% [13%^[20]]); and (c) NaOH, H₂O/*i*PrOH, rt, 1 h (**8**: 6%, three steps [7%^[20]]; **9**: 9%, three steps [10%^[20]])



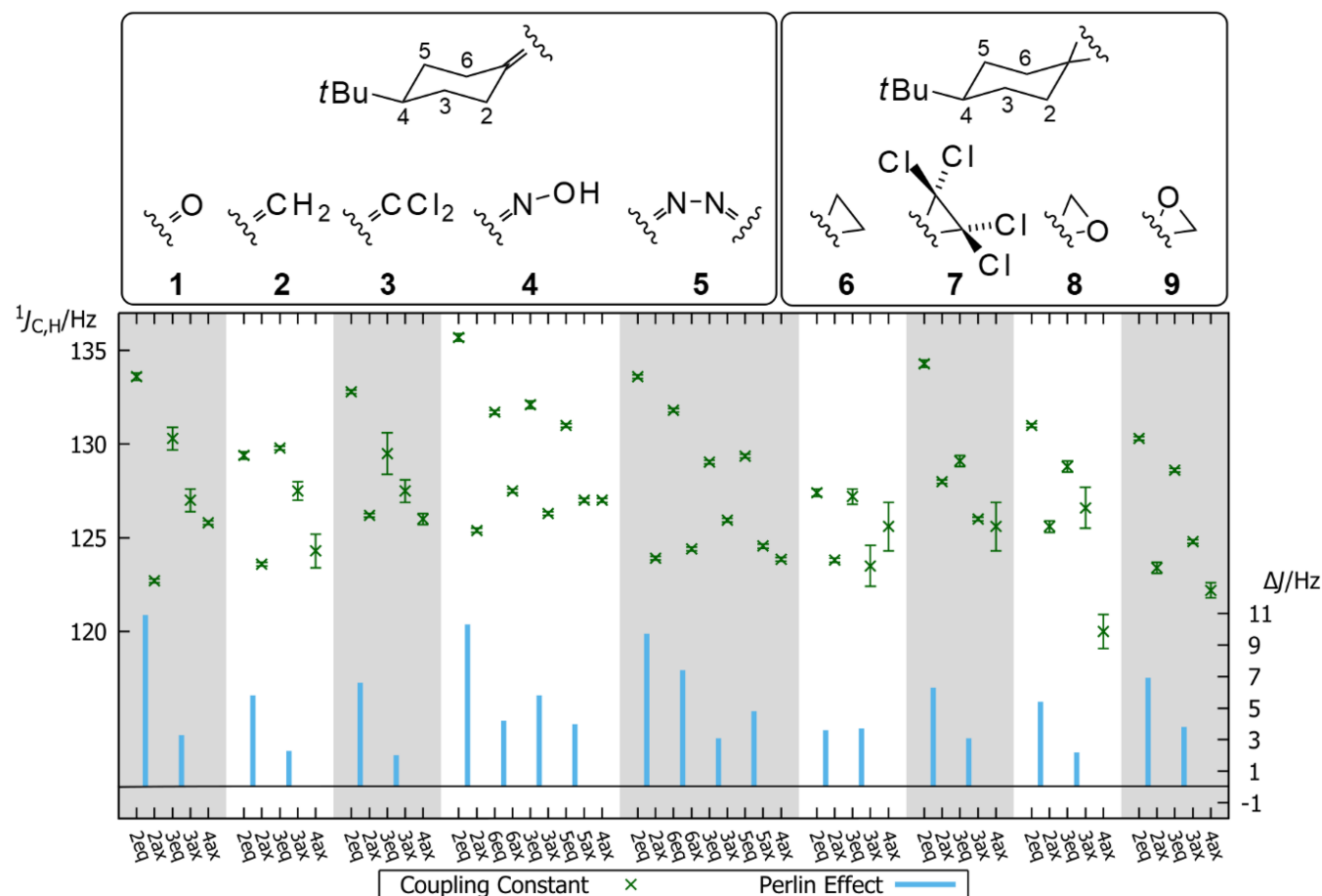


FIGURE 2 Experimental $^1J_{C,H}$ coupling constants of cyclohexane derivatives **1–9** (green data points with error bars; left scale) and Perlin effects ($^1J_{C,Heq} - ^1J_{C,Hax}$; blue bars; right scale)

larger than those of the axial bonds. For none of the carbons, a reversed Perlin effect was observed as has, for example, been noted for thianes,^[3] 1,3-dithianes,^[6d,e] and related compounds.^[6e] The most pronounced Perlin effects were measured for cyclohexanone **1** and for the condensation products **4** and **5**, whereas they are significantly smaller in alkenes **2** and **3**. Different coupling constants are observed for both α (and β) positions in the non-symmetric compounds **4** and **5**. The lone pairs at the nitrogen atoms as well as the N–O and N–N bonds obviously have a significant influence, which is discussed in the next section. Perlin effects are somewhat smaller at the α positions of spiro compounds **6–9**, especially in spirooctane **6**. Perlin effects at the β positions are smaller than those at the α positions and are quite similar for all investigated compounds **1–9**. Homoanomeric effects, as have been proposed by Alabugin et al., seem to play a negligible role in these substrates.^[22] This is quite obvious especially for compounds **6–9** considering that the endocyclic lone pairs in the three-membered rings are depleted of p character and are hence relatively weak donors.^[23]

4 | NBO ANALYSES OF CYCLOHEXANONE AND METHYLENOCYCLOHEXANE DERIVATIVES 1–5

A commonly used tool for the quantification of stereoelectronic interactions is the natural bond orbital (NBO) method developed by Weinhold and coworkers,^[24] where the canonical delocalized Hartree–Fock molecular orbitals (MOs) are transformed into localized hybrid orbitals (NBOs). The interactions between filled and antibonding or Rydberg orbitals quantify the energetic contribution of a distinct stereoelectronic effect. The orbital overlap (F_{ij}) as given in the standard NBO output and the energy difference (ΔE) are the basis for the $E(2)$ resonance energies, in which neither competing resonance interactions nor changes of the dipole moment are considered. More meaningful values are obtained by deletion of the corresponding off-diagonal elements of the Fock matrix in the NBO basis. It has already been noted by Alabugin,^[6e] by Juaristi,^[6f] and by us^[3] that there is no simple and evident correlation between resonance

energies obtained from NBO analyses and coupling constants. Contreras et al. investigated the influence of stereoelectronic effects on coupling constants^[25] to get deeper insight into the theoretical interrelation. They were able to explain both the missing of correlations and some of the observed trends. They split Fermi contact interactions (which is the dominant coupling mechanism) into orbital contributions of occupied and unoccupied localized MOs (LMOs). They thus obtained contributions to the coupling constant of a C—H bond, which are due to the respective σ orbital (J^b , with b: bond), due to the respective σ^* orbital (J^{ab} ; ab: antibond), or due to further bonds at the coupling atoms (J^{ob} ; ob: other bond). Contreras and coworkers could take advantage of well-chosen model compounds, in which the “other bonds” are symmetry equivalent. The influence of “other bonds” is plausible: when the s character in an “other bond’s” hybrid orbital is altered by resonance, this must have an immediate effect on the hybridization of the respective atom’s other bonds—there is a total of only one 2s orbital for every carbon. As the s character is significant for the Fermi contact, this must have an influence on the coupling constants. The subtle interplay of hybridization and hyperconjugation has similarly been reported in other systems and is of relevance, for example, in the blue-shifting hydrogen bonding.^[26]

We performed quantum chemical investigations with *tert*-butyl-substituted substrates **1–9**, but Martínez-Mayorga et al. have already performed similar calculations (calculation of coupling constants and NBO analyses) with the parent cyclohexanone and methylenecyclohexane.^[6f] In full agreement with the experimental data obtained by us, they observed a larger Perlin effect for cyclohexanone. They argued that π^* of the carbonyl group is a better acceptor as compared with that of the C=C bond in methylenecyclohexane. Nevertheless, this was in dissent with the resonance energies (E_{del}) they obtained from NBO analyses; here, the $\sigma_{\text{C}_2, \text{Hax}} \rightarrow \pi^*$ interaction in methylenecyclohexane turned out to be more pronounced. They assumed the C1—C2 bond of the alkene to be shorter than that of cyclohexanone, which would lead to an increased overlap. Actually, the C1—C2 bond of ketone **1** is slightly longer than

that in alkene **2**, (C1—C2 in **1**: 152 pm, **2**: 151 pm) due to an $n_{\text{O}} \rightarrow \sigma^*_{\text{C}_1, \text{C}_2}$ interaction. However, the $\sigma_{\text{C}_2, \text{Hax}} \rightarrow \pi^*$ interaction is still stronger in ketone **1**, because the expanded orbital lobe at carbon C1 of the polarized π^* orbital allows for a better overlap (Figure 3a). Consequently, the $E(2)$ energy for the $\sigma_{\text{C}_2, \text{Hax}} \rightarrow \pi^*$ interaction is calculated to be higher for ketone **1** than for alkene **2**. An inverted trend for the E_{del} energies can be explained with the higher dipole moment of the ketone. This dipole would be further increased by transfer of electron density into π^* (Figure 3b). Without competing influence of “other bond’s” resonances, the $^1J_{\text{C}_2, \text{Hax}}$ coupling constant in alkene **2** could be expected to be smaller than that of ketone **1**. Nevertheless, the $n_{\text{O}} \rightarrow \sigma^*_{\text{C}_1, \text{C}_2}$ interaction in **1** leads to an increased s character of the C—C bond and thus to a reduced s character of the adjacent C—H bonds, ultimately reducing the coupling. The smaller Perlin effect in the α positions of alkene **2** cannot be explained with a resonance interaction of the axial C—H bond but has its origin mainly in that of the equatorial C—H bonds. The $\sigma_{\text{C}_2, \text{Heq}} \rightarrow \sigma^*_{\text{C}_1, \text{C}_6}$ interaction in ketone **1** competes with an $n_{\text{O}} \rightarrow \sigma^*_{\text{C}_1, \text{C}_6}$ interaction (Figure 3c) and is thus smaller than that in alkene **2**. Consequently, the equatorial C2—H bond in ketone **1** is stronger and a larger coupling constant (133.6 Hz as compared with 129.4 Hz in **2**) and thus a stronger Perlin effect is observed.

The coupling constants in the α positions of dichloroalkene **3** are larger than those of alkene **2**. Both the σ^* and the π^* orbital turned out to be poor acceptors in the interaction with the $\sigma_{\text{C}_2, \text{Hax}}$ orbitals because both bonds are significantly involved in interactions with lone pairs at the chlorine atoms. Surprisingly, the $\sigma_{\text{C}_2, \text{Heq}} \rightarrow \sigma^*_{\text{C}_1, \text{C}_6}$ is similarly poor (4.7 kcal/mol) in the chlorinated compound **3** and in the parent compound **2** (5.6 kcal/mol). Significant differences are observed for the C1—C6 bonds of alkenes **2** and **3** (Table 1). In dichloroalkene **3**, this bond is antiperiplanar to a C—Cl bond, which acts as acceptor in a stereoelectronic interaction and furthermore is inductively electron-withdrawing. This polarizes the C1—C6 bond, where the occupied σ orbital has a larger coefficient at C1 and the σ^* orbital has as larger coefficient at C6. The latter is distal of the $\text{C}_{2, \text{Heq}}$ bond; a significant overlap is thus not possible. The

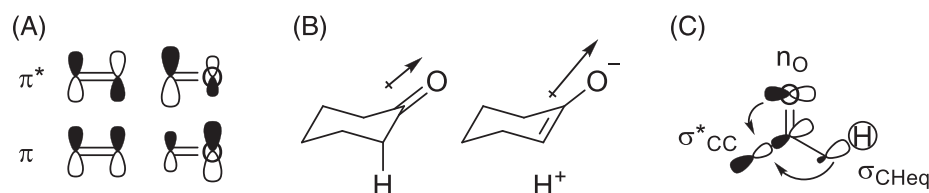


FIGURE 3 (a) Polarization in the C=O bond leads to orbital lobes of different sizes; (b) the $\sigma_{\text{C}_2, \text{Hax}} \rightarrow \pi^*$ interaction would lead to an increased dipole moment; and (c) the donor ability of the equatorial σ_{CH} orbital competes with that of the n_{O} orbital

C1		C2		Occupation	
Coefficients σ/σ^*	%s	Coefficients σ/σ^*	%s	σ	σ^*
49.6/50.4	30.5	50.4/49.6	29.1	1.973	0.029
51.4/48.7	31.0	48.7/51.4	27.1	1.960	0.026



TABLE 1 Structural differences in the C1–C2 bonds of alkene **2** and dichloroalkene **3**

polarization furthermore reduces the s character at C2, providing a larger share of the s orbital for the C–H bonds.

Oxime **4** and hydrazone **5** show significant differences of the coupling constants in both branches of the six-membered rings (i.e., C2 vs. C6 and C3 vs. C5). This and the deviating data for the two rotamers of hydrazone **5** suggest a strong dependence of the coupling constants on the respective configuration and on subtle conformational changes. This is further supported by somewhat more pronounced differences between measured and calculated coupling constants in comparison with those of the other investigated compounds. Nevertheless, the trends in the data are consistent. As for cyclohexanone **1**, the Perlin effects at the α positions are distinct, albeit with significant differences for the *syn* and *anti* positions with regard to the double bond's configurations. This again emphasizes the importance of the molecules' dipoles and of additional resonances with participation of seemingly innocent, adjacent bonds. CH₂ groups in positions C6 (*anti* to the heteroatom) show stronger Perlin effects than those at positions C2, especially for oxime **4**. Whereas a $\pi \rightarrow \sigma^*_{C,H_{ax}}$ interaction is dominant for positions C6, it is the inverted $\sigma_{C,H_{ax}} \rightarrow \pi^*$ interaction that is more pronounced for positions C2 (Figure 4a). Both interactions lead to a reduced total dipole moment. Nevertheless, the local dipole in the vicinity of the double-bonded nitrogen atoms is higher in hydrazone **5** than in oxime **4**, because the oxygen's lone pair in the oxime gives rise to an antagonistic local dipole moment (Figure 4b). This has an influence on the donor and on the acceptor abilities of the C–C bonds. As a consequence of the dipole moments, the C1–C6 bond in hydrazone **5** is a better donor in the interaction with the antiperiplanar C2–H_{eq} bond and a worse acceptor than the opposed C1–C2 bond. A reversed effect is operative in oxime **4**, because the donor ability of the C1–C6 bond is reduced by a $\sigma_{C1,C6} \rightarrow \sigma^*_{N,O}$ interaction (Figure 4c).

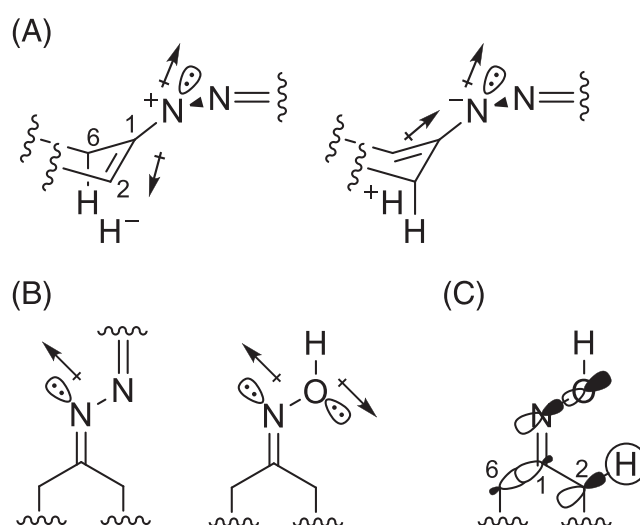


FIGURE 4 (a) In hydrazone **5**, the dipole moment controls whether a C–H bond is predominantly a donor or an acceptor; (b) bond dipole moments compensate each other in oxime **4**; and (c) the acceptor ability of the N–O bond in oxime **4** competes with that of the C2–H_{eq} bond

The stereoelectronic interactions between the π bonds in cyclohexane derivatives **1–5** and the axial C–H bonds at the adjacent carbon atoms (C2 and C6) are summarized in Table 2. Both the $\pi \rightarrow \sigma^*_{C,H_{ax}}$ and the converse $\sigma_{C,H_{ax}} \rightarrow \pi^*$ interactions would reduce the bond order of the respective C–H_{ax} bond. Interaction with the π bond as donor (left column) is somewhat less pronounced in ketone **1** and in alkenes **2** and **3** than the respective interactions with the π bond as acceptor (right column). An inverted (or at least slightly less pronounced) effect is observed for oxime **4** and for hydrazone **5**. The somewhat higher donor ability of the C=N π bond in the latter compounds is possibly due to an effect caused by the neighboring O and N atoms, respectively. This effect, which could be related to the α effect,^[27] is stronger in oxime **4** than in hydrazone **5**, possibly due to the fact that the

TABLE 2 Stereoelectronic interactions of the π bonds in cyclohexane derivatives **1–5**, **13**, and **14**

Compound	=X	$\pi \rightarrow \sigma^*_{\text{C,Hax}}$ (kcal/mol)	$\sigma_{\text{C,Hax}} \rightarrow \pi^*$ (kcal/mol)
1	=O	5.1	6.1
2	=CH ₂	5.8	7.5
3	=CCl ₂	5.3	6.8
4	=NOH	5.9 ^a , 7.6 ^b	6.0 ^a , 4.6 ^b
5	=N=CR ₂	5.1 ^a , 6.4 ^b	6.0 ^a , 5.0 ^b
13^c	=NCH ₃	5.4 ^a , 6.4 ^b	6.6 ^a , 5.8 ^b
14^c	=NNH ₂	6.1 ^a , 7.4 ^b	5.9 ^a , 5.0 ^b

^aC2–H_{ax} (*syn* to the substituent at the =N atom).^bC6–H_{ax} (*anti* to the substituent at the =N atom).^cStereoelectronic interactions in imine **13** and hydrazone **14** were calculated for comparison.

neighboring nitrogen in **5** is part of a further π bond. We checked this by calculating these stereoelectronic interactions in two reference compounds **13** and **14**, in which either no α -like effect is possible (in imine **13**) or the nitrogen causing this effect is no longer part of a double bond (in hydrazone **14**). It turned out that oxime **4** and the simple hydrazone **14** similarly show strong $\pi \rightarrow \sigma^*_{\text{C,Hax}}$ interactions; a clear α -like effect can here be assumed. This interaction is significantly smaller in hydrazone **5** and in imine **13**, most likely due to a smaller or even non-existing α -like effect.

5 | NBO ANALYSES OF SPIRO COMPOUNDS 6–9

Two models for the description of the bonding in three-membered rings are well established: the Walsh model,

TABLE 3 Orbital models in cyclopropane and ethene

Model (orbitals)	Cyclopropane	Ethene	Bond types
Walsh ($sp^2 + p$)			$\sigma + \pi$
Coulson–Moffitt ($2 \times sp^5$)			τ

in which the bonds are constructed from sp^2 and p orbitals,^[28] and the model from Coulson and Moffitt, who suggested bent bonds built from hybrid orbitals.^[29] The similarities of cyclopropanes and ethene and of oxiranes and carbonyl compounds have been emphasized repeatedly.^[28–30] The features of both models are given in Table 3 for cyclopropane and for ethene.

In this analogy, it is not astonishing that both the solvolysis of allylic compounds and of cyclopropylmethyl substrates proceed with remarkably high reaction rates.^[31] The intermediate carbocations are stabilized by delocalization of the positive charge into the neighboring π system.^[32] In that way, the delocalization of carbanionic^[33] or radical centers^[34] into C=C double bonds leads to a stabilization of the respective allyl anions and radicals. However, cyclopropylmethyl radicals are not similarly stabilized. The bond dissociation energy of the respective C–H bond in methylcyclopropane

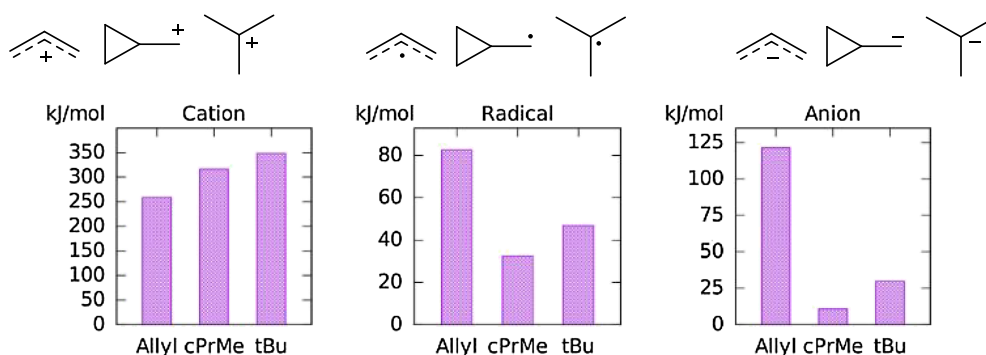


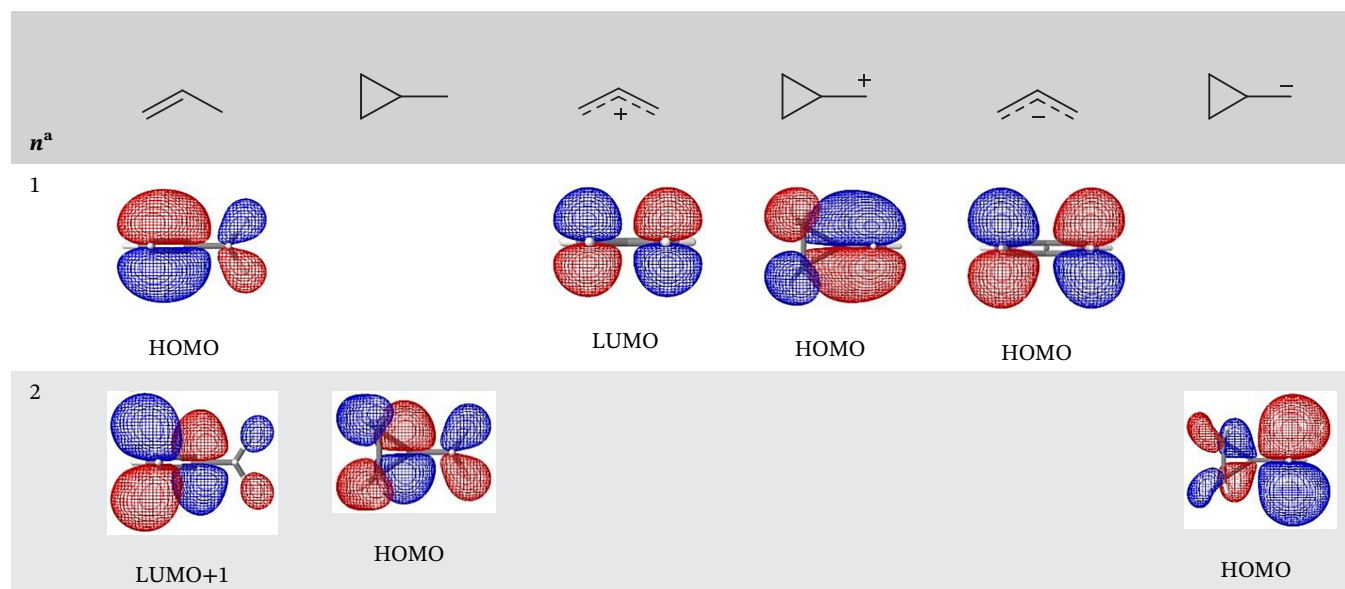
FIGURE 5 Stabilization of reactive intermediates relative to the respective methyl species [B3LYP/6-311++G(d,p)]

(412 kJ/mol) is only slightly lower than that of the Et—H bond (420 kJ/mol).^[35] Likewise, the stabilization of carbanionic centers by a cyclopropyl group is much smaller than that in an allyl anion.^[36] To quantify these findings, we calculated the energies of cations, anions, and radicals of propene, methylcyclopropane, and isobutene. We chose the methyl cation, its anion, and its radical as references for all calculations (Figure 5). Conformations of the cyclopropylmethyl species were chosen for these calculations, in which the empty or singly occupied p orbital, or the lone pair, are in bisectic orientations.

Whereas the cyclopropylmethyl cation is even better stabilized than the allyl cation, the stabilization of the respective cyclopropylmethyl radical is significantly less pronounced than that in the allyl radical. Hardly any stabilization is observed for the cyclopropylmethyl anion. Obviously, the cyclopropyl group is a good donor in a positive hyperconjugation, whereas it is a poor acceptor in a negative hyperconjugation. Inspection of the MOs makes this behavior understandable. Because the π

system of methylcyclopropane contains two electrons more than propene, the HOMO of the former needs to have one nodal plane more than the latter. Actually, the methylcyclopropyl cation's HOMO is isolobal to the allyl anion's HOMO (and to the allyl cation's LUMO). Similarly, the HOMO of the neutral methylcyclopropane is isolobal to the LUMO+1 of propene (Table 4). Consequently, in neutral hyperconjugation, the cyclopropyl unit in **6** should be a worse acceptor than the double bond in alkene **2**. The NBO software considers a double bond to be built from sp^2 and p orbitals, whereas a cyclopropane is here constructed from sp^5 hybrid orbitals. To compare the acceptor quality of both systems, it is thus essential to additionally consider the acceptor ability of the double bond's σ^* orbital. A comparison of the respective deletion energies (E_{del}) confirms this assumption: As compared with a C=C double bond, the cyclopropyl unit is a poor acceptor and a better donor. The chlorinated spiro compound **7** shows a stronger Perlin effect at C2 than the parent spirooctane **6**. This can similarly be traced back to the influence of bond polarizations, which

TABLE 4 π -Type orbitals in allyl and cyclopropylmethyl species



^aNumber of nodal planes in the π system.

has already been discussed for alkenes **2** and **3** (*vide supra*).

A comparison of the epoxides **8** and **9** with cyclohexanone **1** shows that the C=O double bond of the latter is a better acceptor *and* a better donor. The bond order of the axial C–H bonds in the epoxides is not notably reduced, and the Perlin effect in these compounds is smaller. The small differences in the coupling constants and in the Perlin effects of **8** and **9** are most probably due to dipole effects and to an $n_{\text{O}} \rightarrow \sigma_{\text{C}_2, \text{H}_{\text{ax}}}^*$ interaction in epoxide **9**.

6 | COMPARISON OF EXPERIMENTAL AND CALCULATED COUPLING CONSTANTS

We previously reported the investigation of Perlin effects in conformationally constrained thiane-derived compounds.^[3] These were determined with the very same methods as reported herein. Together with the data collected in the now presented study of cyclohexanone derivatives, we can provide a sufficiently large dataset to

TABLE 5 Correlation of calculated and measured coupling constants

Method	Correlation	Perlin effects (PE)
GIAO B3LYP/6-311+ +G(d,p)// B3LYP/6-311+ +G(d,p)		
GIAO BP86/aug-cc- pVTZ-J// B3LYP/6-311+ +G(d,p)		
GIAO CPCM- B3LYP/6-311+ +G(d,p)// CPCM- B3LYP/6-311+ +G(d,p)		
GIAO CPCM-BP86/ aug-cc-pVTZ- J// CPCM- B3LYP/6-311+ +G(d,p)		

compare experimental and calculated values. For the statistical evaluation, compounds with a certain degree of flexibility such as hydrazone **5** and oxime **4** as well as thiane derivatives with *N*-tosylsulfilimine (S=NTs) functionalities were omitted. A chart depicting all compounds used for this survey is given in the supporting information. 1J coupling constants of these compounds were calculated on the B3LYP/6-311++G(d,p) level of theory. We additionally optimized all structures using the CPCM solvation model in chloroform and again calculated the coupling constants. In previous work, it seemed to be common to calculate NMR parameters using dedicated basis sets. Maximoff et al. identified the aug-cc-pVTZ-J basis set with the BP86 functional to be superior to B3LYP.^[37] Consequently, we compared results obtained with this basis set with those calculated with B3LYP-optimized structures (with and without solvation). We used aug-cc-pVTZ-J for all first row elements, whereas aug-cc-pVTZ was used for sulfur and chlorine. We studied the correlation of calculated and experimental values as well as the deviation of calculated and observed Perlin effects (Table 5).

Seemingly, the overall quality of the correlations is very satisfactory. R^2 values (0.97–0.98) and the mean average errors (MAEs; 0.9–1.0) suggest a strong linear correlation. It should be mentioned that we applied an error weighting (using $1/S$). It turned out that no significant improvement is obvious with the BP86/aug-cc-pVTZ-J functional. Astonishingly, a solvent correction results in slightly increased errors and smaller coefficients of determination. A linear correction of calculated coupling constants, as commonly used for chemical shift calculations, seems reasonable, especially when future experiments complement the database for correlation studies.

A deviating picture can be seen when Perlin effects are studied. Slightly improved results are observed with the more expensive method and the scattering is significantly reduced when solvent correction is applied. If one aims for a prediction of Perlin effects as precise as possible, the use of solvent correction seems to be mandatory. However, the investigation of stereoelectronic effects based on calculated coupling constants turned out to be possible without the solvent correction.

7 | CONCLUSION

We investigated the influences of stereoelectronic interactions on Perlin effects in conformationally constrained cyclohexanones and structurally related spiro compounds. Careful analysis of NMR spectroscopic data shed light on the crucial donor/acceptor

interactions and allowed to rationalize the observed coupling constants. Calculation of NBO deletion energies turned out to be significantly more meaningful than a simple consideration of $E(2)$ energies, when competing interactions are operative in the investigated compounds. The interplay of delocalization and dipole effects is especially obvious in oxime **4** and hydrazone **5**. The investigation of spiro compounds revealed the influence of additional π -type electrons: donor abilities are preserved, whereas acceptor abilities are significantly reduced. A comparison of experimental and calculated coupling constants proved that the B3LYP functional in combination with Pople basis sets gives an adequate correlation.

8 | EXPERIMENTAL

8.1 | NMR spectroscopic investigations

$^1J_{C,H}$ coupling constants of the cyclohexane-derived compounds **1–9** were measured on a Bruker Avance III HD 500-MHz spectrometer using CLIP-HSQC experiments^[38] and analyzed using the TopSpin software package.^[39] CLIP-HSQC spectra result in clean in-phase doublets in the directly detected dimension, so that accurate coupling constants can be determined without further phase correction. Spectra were acquired using broadband BEBOP excitation,^[40] BIBOP inversion,^[41] and BURBOP refocusing pulses.^[42] When a signal overlap obscured the coupling constants, we used ω_1 -iINEPT experiments with BIP inversion pulses during the BIRD-element^[43] for clarification.^[44] Number of scans as well as acquisition times and spectral widths were optimized for each compound individually. In all cases, digital resolution in the dimension with coupling evolution was below 0.1 Hz for CLIP-HSQC experiments and below 1.0 Hz for the ω_1 -iINEPT experiments. Due to highly symmetric multiplets and sufficient chemical shift difference of coupling partners, second-order contributions could be neglected in most cases. The individually estimated experimental errors of the coupling constants were generally on the order of the digital resolution, sometimes even below (see Figure 2).

8.2 | Quantum chemical calculations

All structures were optimized at the B3LYP^[45]/6-311++G(d,p)^[46] level by using the Gaussian 09 software package.^[47] Coupling constants were calculated with the gauge-including atomic orbital (GIAO) method^[48] either at the same level or with the BP86^[49]/aug-cc-pVTZ-J^[50]

functional. Solvent was modeled with the CPCM-SCRF method with chloroform as solvent.^[51] The NBO 3.1 software for NBO analyses^[24] was used as implemented in Gaussian 09.

8.3 | Synthetic procedures: General

Compound **1** was purchased (Sigma-Aldrich). Et₂O and pentane were distilled from sodium benzophenone ketyl radical prior to use, and CH₂Cl₂ was distilled from CaH₂. All moisture-sensitive reactions were carried out under oxygen-free argon using oven-dried glassware and a vacuum line (Schlenk technique). Flash column chromatography was carried out using Merck silica gel 60 (230–400 mesh), and TLC was carried out by using commercially available Merck F254 pre-coated sheets. Pre-coated TLC plates SIL G-200 (Macherey-Nagel) were used for preparative TLC. Spots were detected by fluorescence quenching and staining in an iodine chamber. NMR spectra were recorded on Bruker Avance AV 300 or Bruker Avance III HD 500 spectrometers. ¹³C NMR spectra were recorded with broad band decoupling, and signals were assigned by HSQC experiments. The spectra were calibrated using the residual solvent signals. IR spectra were recorded on a Bruker FT-IR spectrometer “Alpha” using ATR on diamond. EI mass spectra were recorded with a Finnigan MAT-95 and APCI spectra were recorded with a Q Exactive Orbitrap (Thermo Fisher). Melting points were measured with an Optimelt MPA100 apparatus and are not corrected.

8.3.1 | 4-(*tert*-Butyl)cyclohexanone (1)

¹H NMR (500 MHz, CDCl₃): δ = 0.91 (s, 9 H, *t*Bu), 1.39–1.53 (m, 3 H, 3-H_{ax}, 5-H_{ax}, 4-H), 2.04–2.11 (m, 2 H, 3-H_{eq}, 5-H_{eq}), 2.39 (d, ²*J* = 14.1 Hz, 2 H, 2-H, 6-H), 2.31 (ddd, ²*J* = 14.1, ³*J* = 13.5, ³*J* = 5.4 Hz, 2 H, 2-H, 6-H); ¹³C NMR (125 MHz, CDCl₃): δ = 27.8 [(CH₃)₃C, C-3, C-5], 32.6 [(CH₃)₃C], 41.5 (C-2, C-6), 46.9 (C-4).

8.3.2 | 1-(*tert*-Butyl)-4-methylenecyclohexane (2)

This compound was prepared in analogy to a published protocol.^[16] BuLi (2.5 M in hexane, 5.8 ml, 14.4 mmol) was added dropwise via a syringe to a solution of Ph₃PMeBr (5.14 g, 14.4 mmol) in anhydrous Et₂O (100 ml) placed in a dried flask equipped with a septum. The mixture turned intensely yellow (ylide formation) and was stirred for 35 min at rt. A solution of

cyclohexanone **1** (2.00 g, 13.0 mmol) in anhydrous Et₂O (~5 ml) was added slowly at rt and a colorless precipitate formed. The mixture was stirred for 20 h and H₂O (~65 mL) was added. The organic layer was separated, dried (Na₂SO₄), concentrated at reduced pressure, and purified by column chromatography (silica gel, cyclohexane/EtOAc, 100:1) to yield alkene **2** (912 mg, 5.99 mmol, 46%) as a yellowish oil. ¹H NMR (500 MHz, CDCl₃): δ = 0.85 (s, 9 H, *t*Bu), 1.04 (dddd, ²*J* = ³*J* = ³*J* = 12.5 Hz, ³*J* = 3.4 Hz, 2 H, 2-H_{ax}, 6-H_{ax}), 1.14 (tt, ³*J* = 11.8 Hz, ³*J* = 2.6 Hz, 1 H, 1-H), 1.86 (br d, ²*J* = 11.8 Hz, 2 H, 2-H_{eq}, 6-H_{eq}), 1.98 (br dd, ²*J* = ³*J* = 12.9 Hz, 2 H, 3-H_{ax}, 5-H_{ax}), 2.33 (br d, ³*J* = 12.9 Hz, 2 H, 3-H_{eq}, 5-H_{eq}), 4.57 (t, ⁴*J* = 1.5 Hz, 2 H, =CH₂); ¹³C NMR (125 MHz, CDCl₃): δ = 27.8 [C (CH₃)₃], 29.1 (C-2, C-6), 32.6 [C (CH₃)₃], 35.5 (C-3, C-5), 48.0 (C-1), 106.2 (=CH₂), 150.5 (C-4). The spectroscopic data are in full agreement with those from the literature.^[52]

8.3.3 | 1-(*tert*-Butyl)-4-(dichloromethylene)cyclohexane (3)

This compound was prepared in analogy to a published protocol.^[17] A flame-dried flask was equipped successively under argon with cyclohexanone **1** (770 mg, 5.00 mmol), PPh₃ (5.24 g, 20.0 mmol), and MeCN (10 ml). CCl₄ (1.0 ml, 1.54 g, 10.0 mmol) was added at 0°C and the mixture was stirred for 75 min at rt, by which it turned yellow and then reddish-brown. Et₂O (25 ml) was added and the mixture was washed with H₂O (2 × 25 ml) and brine (2 × 40 ml). The organic layer was dried (Na₂SO₄), concentrated at reduced pressure, and purified by column chromatography (silica gel, cyclohexane/EtOAc, 100:1) to yield dichloroalkene **3** (662 mg, 2.99 mmol, 96%) as a pale yellow solid. ¹H NMR (500 MHz, CDCl₃): δ = 0.86 (s, 9 H, *t*Bu), 1.08 (dddd, ²*J* = ³*J* = 12.4 Hz, ³*J* = 12.2 Hz, ³*J* = 3.9 Hz, 2 H, 2-H_{ax}, 6-H_{ax}), 1.16 (tt, ³*J* = 12.2 Hz, ³*J* = 2.4 Hz, 1 H, 1-H_{ax}), 1.82–1.91 (m, 4 H, 2-H_{eq}, 6-H_{eq}, 3-H_{ax}, 5-H_{ax}), 2.94 (br d, ²*J* = 12.8 Hz, 2 H, 3-H_{eq}, 5-H_{eq}); ¹³C NMR (125 MHz, CDCl₃): δ 27.6 (C-2, C-6), 27.7 [C (CH₃)₃], 31.8 (C-3, C-5), 32.5 [C (CH₃)₃], 47.7 (C-1), 138.1 (CCl₂), 153.7 (C-4); the peak for CCl₂ is given in the literature at δ = 110.8.^[53]

8.3.4 | 4-(*tert*-Butyl)cyclohexanone oxime (4)

This known compound was prepared according to a published protocol.^[14] A mixture of cyclohexanone **1** (500 mg, 3.24 mmol), H₂NOH·HCl (270 mg, 3.89 mmol), and NaOH (156 mg, 3.89 mmol) was finely grounded in a

mortar (10 min). Grinding was repeated every 4 min for 1 min over a period of 40 min. The mixture was washed with H₂O (~12 ml) and the remnant was dried for 3 h over CaCl₂ and recrystallized from Et₂O/pentane (1:2, ~15 ml, -18°C) to yield **4** (149 mg, 0.880 mmol, 27% [89%–96%^[14]]) as colorless needles. Further product could have been isolated from the mother liquor. ¹H NMR (500 MHz, CDCl₃): δ = 1.86 (s, 9 H, *t*Bu), 1.11–1.29 (m, 3 H, 3-H_{ax}, 5-H_{ax}, 4-H_{ax}), 1.69 (ddd, ²J = ³J = 13.8 Hz, ³J = 5.2 Hz, 1 H, 2-H_{ax}), 1.88–1.96 (m, 2 H, 3-H_{eq}, 5-H_{eq}), 2.05 (ddd, ²J = ³J = 13.2 Hz, ³J = 4.4 Hz, 1 H, 6-H_{ax}), 2.44 (br d, ²J = 14.0 Hz, 1 H, 6-H_{eq}), 3.36 (br d, ²J = 14.4 Hz, 1 H, 2-H_{eq}); ¹³C NMR (125 MHz, CDCl₃): δ = 24.4 (C-2), 26.4 (C-3), 27.7 [(CH₃)₃C, C-5], 32.1 (C-6), 32.6 [(CH₃)₃C], 47.6 (C-4), 161.8 (C-1). The spectroscopic data are in full agreement with those from the literature.^[54]

8.3.5 | 1,2-Bis-[4-(*tert*-butyl)cyclohexylidene]hydrazine (5)

This compound was prepared in analogy to a published protocol.^[15] A solution of cyclohexanone **1** (500 mg, 3.24 mmol) in MeOH (2 ml) was added with stirring at °C to H₂NNH₂·H₂O (~85%, 1.7 ml, 1.67 g, 44.3 mmol) in a Pyrex tube. A colorless precipitate developed and the mixture was stirred for 1 h at 60°C and cooled to rt. CH₂Cl₂ (~10 ml) was added and the layers were separated. The aqueous layer was extracted with CH₂Cl₂ (3 × 5 ml) and the combined organic layers were concentrated at reduced pressure and recrystallized from CH₂Cl₂/pentane (1:2, ~12 ml, -18°C) to yield hydrazone **5** (208 mg, 1.24 mmol, 38%) colorless needles. Further product could have been isolated from the mother liquor. m.p. 174–175°C; ¹H NMR (500 MHz, CDCl₃): δ = 0.87 (s, 18 H, 2 × *t*Bu), 1.09–1.24 (m, 2 H, 5-H_{ax}, 5'-H_{ax}), 1.24–1.34 (m, 4 H, 3-H_{ax}, 3'-H_{ax}, 4-H_{ax}, 4'-H_{ax}), 1.64–1.76 (m, 2 H, 2-H_{ax}, 2'-H_{ax}), 1.87–1.94 (m, 2 H, 5-H_{eq}, 5'-Heq), 1.96–2.04 (m, 2 H, 3-H_{eq}, 3'-Heq), 2.14–2.23 (m, 2 H, 6-H_{ax}, 6'-H_{ax}), 2.49–2.55 (m, 2 H, 6-H_{eq}, 6'-Heq), 3.11–3.19 (m, 2 H, 2-H_{eq}, 2'-Heq); ¹³C NMR (125 MHz, CDCl₃): δ = 27.1, 27.2 (C-5, C-5'), 27.6, 27.6 (C-2, C-2'), 27.7 [2 × (CH₃)₃C], 28.2, 28.3 (C-3, C-3'), 32.5, 32.6 [2 × (CH₃)₃C], 35.5 (C-6, C-6'), 47.7, 47.7 (C-4, C-4'), 166.2, 166.2 (C-1, C-1'); IR (ATR): $\tilde{\nu}$ (cm⁻¹) = 2952, 2860, 1638, 1466, 1439, 1393, 1363, 1343, 1240, 1219, 1176, 984, 951, 916, 774, 570, 427; MS (APSC): *m/z* (%) = 306.3 (22), 305.3 (100), 121.1 (21); HRMS (EI): calcd. for C₂₀H₃₇N₂ [M + H]⁺: 305.2951; found: 305.2944; elemental analysis calcd. for C₂₀H₃₇N₂: C 78.88, H 11.92, N 9.20, found: C 78.53, H 12.09, N 9.18.

8.3.6 | 6-(*tert*-Butyl)-1,1-dichlorospiro[2.5]octane (10)

This compound was prepared in analogy to a published protocol.^[18] A solution of NaOH (458 mg, 11.4 mmol) in H₂O (1 ml) was added to a stirred solution of alkene **2** (150 mg, 0.985 mmol) and Me (CH₂)₁₅NMe₃⁺Br⁻ (CTAB; 12.1 mg, 33.2 μmol) in CHCl₃ (1.53 ml, 2.26 g, 18.9 mmol). The mixture was stirred for 21 h and CH₂Cl₂ (5 ml), H₂O (5 ml), and saturated aqueous NH₄Cl solution (~2 ml) were added. The organic layer was separated, dried (Na₂SO₄), and concentrated at reduced pressure to yield dichlorospiroalkane **10** as a mixture of isomers (~85:15; 133 mg, 0.563 mmol, 57%) as colorless solid. Major isomer: ¹H NMR (500 MHz, CDCl₃): δ = 0.87 (s, 9 H, *t*Bu), 0.98–1.12 (m, 5-H_{ax}, 6-H_{ax}, 7-H_{ax}), 1.16 (s, 2 H, 1-H), 1.52 (d, ²J = 13.3 Hz, 2 H, 4-H_{eq}, 8-H_{eq}), 1.77 (br dd, ²J = ³J = 12.4 Hz, 2 H, 4-H_{ax}, 8-H_{ax}), 1.86 (d, ²J = 9.3 Hz, 2 H, 5-H_{eq}, 7-H_{eq}); ¹³C NMR (125 MHz, CDCl₃): δ = 26.0 (C-5, C-7), 27.7 [C (CH₃)₃], 29.8 (C-3), 31.6 (C-1), 32.5 [C (CH₃)₃], 33.3 (C-4, C-8), 47.5 (C-6); IR (ATR): $\tilde{\nu}$ (cm⁻¹) = 2973, 2917, 2850, 1441, 1427, 1394, 1365, 1275, 1242, 1168, 1046, 961, 883, 821, 755, 665, 535, 463; MS (EI, 20°C): *m/z* (%) = 236.2 (1), 234.2 (2), 219.2 (13), 82.1 (19), 81.1 (12), 80.1 (18), 57.1 (100); HRMS (EI): calcd. for C₁₂H₂₀³⁵Cl₂ [M⁺]: 234.0942; found: 234.0940.

8.3.7 | 6-(*tert*-Butyl)spiro[2.5]octane (6)

This compound was prepared in analogy to a published protocol.^[19] A solution of dichlorospiroalkane **10** (200 mg, 1.30 mmol) in anhydrous Et₂O (~3 ml) was added to lithium (18.7 mg, 2.68 mmol) dissolved at -78°C in liquid NH₃ (4 ml). The cooling bath was removed after 75 min and the mixture was slowly brought to rt. MeOH (1 ml) was added and the mixture was extracted with pentane (3 × 3 ml). The organic layers were dried (Na₂SO₄), concentrated at reduced pressure, purified by preparative TLC (silica gel, pentane, extraction of the product with CDCl₃), and distilled using a short path distillation apparatus to remove residual pentane as azeotrope with CDCl₃ (80°C). A sufficient amount of spiro compound **6** was obtained as a solution in CDCl₃. ¹H NMR (500 MHz, CDCl₃): δ = 0.15 (br dd, ²J = 8.3 Hz, ³J = 5.7 Hz, 2 H, 2-H or 1-H), 0.24 (dd, ²J = 8.6 Hz, ³J = 5.5 Hz, 2 H, 1-H or 2-H), 0.80–0.90 (m, 2 H, 4-H_{eq}, 8-H_{eq}), 0.86 (s, 9 H, *t*Bu), 0.99 (br t, ³J = 11.9 Hz, 1 H, 6-H_{ax}), 1.12 (dddd, ²J = ³J = ³J = 12.7 Hz, ³J = 3.2 Hz, 2 H, 5-H_{ax}, 7-H_{ax}), 1.67–1.74 (m, 4 H, 4-H_{ax}, 8-H_{ax}, 5-H_{eq}, 7-H_{eq}); ¹³C NMR (125 MHz, CDCl₃): δ = 11.6 (C-1 or C-2), 12.4 (C-2 or C-1), 19.1 (C-3), 26.5 (C-5, C-7), 27.7 [C (CH₃)₃], 32.5 [C (CH₃)₃], 36.2 (C-4, C-8), 48.0 (C-6).

8.3.8 | 6-(*tert*-Butyl)-1,1,2,2-tetrachlorospiro[2.5]octane (7)

This compound was prepared in analogy to a published protocol.^[18] A solution of NaOH (210 mg, 5.25 mmol) in H₂O (0.5 ml) was added to a stirred solution of dichloroalkene **3** (100 mg, 0.452 mmol) and Me (CH₂)₁₅NMe₃⁺Br⁻ (CTAB; 6.00 mg, 15.0 μmol) in CHCl₃ (0.703 ml, 1.04 g, 8.68 mmol). The mixture was stirred for 21 h and CH₂Cl₂ (5 ml), H₂O (5 ml), and saturated aqueous NH₄Cl solution (~2 ml) were added. The organic layer was separated, dried (Na₂SO₄), concentrated at reduced pressure, and purified by bulb-to-bulb distillation (30 mbar, 100°C) to yield tetrachlorospiroalkane **7** (47.3 mg, 0.156 mmol, 35%) as colorless crystals. m.p. 115°C; ¹H NMR (500 MHz, CDCl₃): δ = 0.89 (s, 9 H, *t*Bu), 1.08 (tt, ³J = 12.6 Hz, ³J = 2.5 Hz, 1 H, 6-H); 1.16 (dddd, ²J = ³J = 12.9 Hz, ³J = 12.6 Hz, ³J = 2.9 Hz, 2 H, 5-H_{ax}, 7-H_{ax}), 1.67 (ddd, ²J = ³J = 13.1 Hz, ³J = 2.3 Hz, 2 H, 4-H_{ax}, 8-H_{ax}), 1.88 (br d, ²J = 12.9 Hz, 2 H, 5-H_{eq}, 7-H_{eq}), 1.99 (br d, ²J = 13.5 Hz, 2 H, 4-H_{eq}, 8-H_{eq}); ¹³C NMR (125 MHz, CDCl₃): δ = 25.5 (C-5, C-7), 27.7 [C (CH₃)₃], 31.6 (C-4, C-8), 32.5 [C (CH₃)₃], 41.2 (C-3), 47.1 (C-6), 72.0 (C-1 or C-2), 72.7 (C-2 or C-1); IR (ATR): $\tilde{\nu}$ (cm⁻¹) = 2962, 2859, 1437, 1395, 1361, 1254, 1172, 1027, 977, 950, 934, 897, 838, 771, 724, 665, 610, 539, 482, 410 cm⁻¹; MS (EI, 20°C): *m/z* (%) = 306 (1), 304 (2), 302 (1) [M⁺], 291 (3), 289 (6), 267 (3), 251 (4), 233 (8), 231 (12), 211 (7), 181 (8), 175 (9), 161 (5), 131 (7), 125 (3), 91 (3), 83 (4), 69 (17), 57 (100); HRMS (EI): calcd. for C₁₂H₁₈³⁷Cl₂ [M⁺]: 302.0163; found: 302.0164.

8.3.9 | (1*s*,4*s*)-1-Bromo-4-(*tert*-butyl)cyclohexyl methanol (**11**) and (1*s*,4*s*)-1-(bromomethyl)-4-(*tert*-butyl)cyclohexan-1-ol (**12**)

Epoxides **8** and **9**^[20] and bromohydrins **11** and **12**^[55] were prepared in analogy to published protocols. Cyclohexanone **1** (2.00 g, 13.0 mmol) was added at rt to a stirred solution of Me₃SI (4.45 g, 21.8 mmol) in anhydrous DMSO (22 ml). A solution of KO*t*Bu (2.56 g, 22.8 mmol) in anhydrous DMSO (14 ml) was added dropwise and the mixture was stirred for 21 h at rt. H₂O (60 ml) was added and the mixture was extracted with Et₂O (3 × 30 ml). The combined organic layers were washed with H₂O (30 ml), dried (Na₂SO₄), and concentrated at reduced pressure to yield a mixture of epoxides **8** and **9**.

Me₂SBr⁺Br⁻ (BDMS,^[21] 2.88 g, 13.0 mmol) was added to a solution of these epoxides in anhydrous MeCN

(65 ml) and the mixture was stirred for 20 min at rt. H₂O (130 ml) was added and the mixture was extracted with EtOAc (3 × 65 ml). The combined organic layers were dried (Na₂SO₄), concentrated at reduced pressure, and purified by column chromatography (silica gel, cyclohexane/EtOAc, 10:1) to yield bromohydrins **11** (274 mg, 1.10 mmol, 8% [Lit: 9%^[20]]) and **12** (311 mg, 1.25 mmol, 10% [Lit: 13%^[20]]) as yellow oils. **11**: ¹H NMR (300 MHz, CDCl₃): δ = 0.86 (s, 9 H, *t*Bu), 0.93–1.07 (m, 2 H), 1.17–1.30 (m, 1 H), 1.49–1.62 (m, 2 H), 1.69–1.78 (m, 2 H), 2.00 (m, 2 H), 2.14 (br s, 1 H), 3.63 (br s, 2 H). **12**: ¹H NMR (300 MHz, CDCl₃): δ = 0.87 (s, 9 H, *t*Bu), 0.89–0.99 (m, 2 H), 1.29–1.38 (m, 4 H), 1.59–1.70 (m, 2 H), 1.80–1.89 (m, 2 H), 3.42 (br s, 1H). The spectroscopic data are in full agreement with those from the literature.^[20]

8.3.10 | (3*r*,6*r*)-6-(*tert*-Butyl)-1-oxaspiro[2.5]octane (**8**)

This compound was prepared in analogy to a published protocol.^[20] NaOH solution (10%, 0.5 ml, 44.0 mg, 1.10 mmol) was added dropwise with stirring to a solution of bromohydrin **11** (311 mg, 1.25 mmol) in H₂O/*i*PrOH (2:3, 10 ml). The mixture was stirred for 55 min and extracted with pentane (3 × 7 ml). The combined organic layers were washed with H₂O (3 × 7 ml), dried (Na₂SO₄), concentrated at reduced pressure, and purified by column chromatography (silica gel, cyclohexane/EtOAc, 50:1) to yield epoxide **8** (140 mg, 0.832 mmol, 6% [7%^[20]]) as a colorless oil. ¹H NMR (500 MHz, CDCl₃): δ = 0.88 (s, 9 H, *t*Bu), 1.08 (tt, ³J = 11.9 Hz, ³J = 2.6 Hz, 1 H, 6-H), 1.19 (dddd, ²J = ³J = ³J = 12.6 Hz, ³J = 3.1 Hz, 2 H, 5-H_{ax}, 7-H_{ax}), 1.32 (br d, ²J = 12.5 Hz, 2 H, 4-H_{eq}, 8-H_{eq}), 1.84 (dd, ²J = 12.9 Hz, ³J = 3.5 Hz, 2 H, 4-H_{ax}, 8-H_{ax}), 1.91 (br d, ²J = 13.2 Hz, 2 H, 5-H_{eq}, 7-H_{eq}), 2.59 (s, 2 H, 2-H); ¹³C NMR (125 MHz, CDCl₃): δ = 26.8 (C-5, C-7), 27.8 [C (CH₃)₃], 32.5 [C (CH₃)₃], 34.1 (C-4, C-8), 47.3 (C-6), 55.3 (C-2), 60.0 (C-3). The spectroscopic data are in full agreement with those from the literature.^[20]

8.3.11 | (3*s*,6*s*)-6-(*tert*-Butyl)-1-oxaspiro[2.5]octane (**9**)

This compound was prepared in analogy to a published protocol.^[20] NaOH solution (10%, 0.6 ml, 50.0 mg, 1.25 mmol) was added dropwise with stirring to a solution of bromohydrin **12** (311 mg, 1.25 mmol) in H₂O/*i*PrOH (2:3, 10 ml). The mixture was stirred for 55 min

and extracted with pentane (3 × 7 ml). The combined organic layers were washed with H₂O (3 × 7 ml), dried (Na₂SO₄), concentrated at reduced pressure, and purified by column chromatography (silica gel, cyclohexane/EtOAc, 50:1) to yield epoxide **9** (192 mg, 1.14 mmol, 9% [10%^[20]]) as a colorless oil. ¹H NMR (500 MHz, CDCl₃): δ = 0.88 (s, 9 H, tBu), 1.06 (tt, ³J = 11.9 Hz, ³J = 2.8 Hz, 1 H, 6-H), 1.29 (br dd, ²J = 14.0 Hz, ³J = 13.0 Hz, 2 H, 4-H_{eq}, 8-H_{eq}), 1.36 (dddd, ³J = 13 Hz, ²J = ³J = 12.8 Hz, ³J = 3.0 Hz, 2 H, 5-H_{ax}, 7-H_{ax}), 1.79 (br d, ²J = 12.6 Hz, 2 H, 5-H_{eq}, 7-H_{eq}), 1.86 (ddd, ²J = ³J = 13.4 Hz, ³J = 3.9 Hz, 2 H, 4-H_{ax}, 8-H_{ax}), 2.63 (s, 2 H, 2-H); ¹³C NMR (125 MHz, CDCl₃): δ = 25.0 (C-5, C-7), 27.8 [C (CH₃)₃], 32.7 [C (CH₃)₃], 33.6 (C-4, C-8), 47.3 (C-6), 54.0 (C-2), 58.5 (C-3). The spectroscopic data are in full agreement with those from the literature.^[20]

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