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Epimerization of *trans*-Cycloalkenes with the X–C=C–SeR*-Unit – The Steric Demand of X = H, F, Cl, Br, I, Me, Et and CF_3

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Dedicated to Professor Konrad Seppelt

Trans-cycloalkenes with the X–C=C–SeR*-unit and ring sizes from 9 to 20 have been synthesized. R* bonding the selenium atom is the chiral (S)-*o*-(1-Methoxypropyl)phenyl-moiety, and X=H, F, Cl, Br, I, Me, Et and CF_3. The planar-chiral trans-cycloalkenes in combination with the chiral residue R* exist as two diastereomers. These can be distinguished in principle by NMR spectroscopy. Here, we have studied the epimerization of the trans-cycloalkenes, i.e., the 180° rotation of the X–C=C-unit through the cavity of the ring. The measurements were done with variable temperature ^{13}C NMR spectroscopy within the range from −110 to 140 °C. The obtained values of the Gibbs energy of activation $\Delta G^{\neq}_C$ depend strongly on the ring size. Furthermore, the $\Delta G^{\neq}_C$ values show dramatic steric effects due to the groups X. The steric requirement of X increases in the series $H \ll F \ll Cl < Me < Br < I < Et < CF_3$. Here, F is significantly larger than H, and CF_3 is larger than Et. The corresponding *i*Pr-compounds could not be synthesized. The transition state structures of the ring inversion for ring sizes 8–20 were calculated at the DFT level of theory.

Introduction

We investigated the reagents R_2Se_2/XeF_2, RSe–EMe_3/XeF_2 (E=Si, Ge, Sn, Pb) and PhSeOTf/$Et_3N \cdot 3HF$ (Tf=CF_3SO_2) as RSeF equivalents in additions to acetylenes. This allowed us to synthesize fluoro(organylseleno)olefins.[1] In addition, we were also able to detect and isolate for the first time the unstable selenenyl fluorides RSeF,[2] and selenirenium and tellurirenium salts as intermediates.[3] For seleniranium and telluriranium salts, and for attempts to dealkylate thiiranium, seleniranium and thiirenium salts, see ref. [4]. Crystal structure analyses verify the *trans* addition of [RSeF] to acetylenes,[1b,c,5] just like it had been found for additions of RSeCl, RSeBr and [RSeI].[6] Cycloalkynes also undergo the addition with [RSeF] and give *trans*-fluoro(organylseleno)cycloalkenes.[1a,d] *trans*-Cycloalkenes show planar chirality. Cope et al. were able for the first time to separate *trans*-cyclooctene, *cis,trans*-1,5-cyclooctadiene, *trans*-cyclononene and *trans*-cyclodecene into their enantiomers. In some cases, they determined the absolute configuration,[7] see also the ref. [8,9] and the overviews in ref. [10]. In the case of *trans*-cyclononene and *trans*-cyclodecene rapid racemization occurs already at room temperature.[7d] The inversion of configuration results from rotation of the planar fragment –CH=CH– by 180° through the cavity of the ring. As expected, alkyl groups on the olefinic C atoms increase the inversion barrier, thus *trans*-1,2-dimethyl-cyclodecene, *trans*-1,2-dimethyl-cycloundecene and *trans*-1,2-dipentyl-cyclododecene are configurationally stable.[9c,d]

The idea for the herein present study was to investigate *trans*-cycloalkenes which possess a X–C=C–SeR* fragment and a chiral group R* with a defined configuration at the Se atom. Depending on the configuration of the *trans*-cycloalkene ring, these molecules exist as two diastereomers. In NMR spectroscopy, these two diastereomers must differ in principle.

Therefore, the enantiomerization of the *trans*-cycloalkene part of molecule can be measured. Enantiomerization means here the 180° rotation of the substituent X through the cavity of the ring. For the whole molecule with the group R* this process is an epimerization. For a suitable ring size *n*, ^{13}C and ^{77}Se NMR signals of these compounds should split depending on X with decreasing temperature. Alternatively, split signals should coalesce as the temperature increases (Scheme 1).

The results obtained can significantly expand the knowledge of the intramolecular dynamics of *trans*-cycloalkenes. In addition, important information on the spatial requirements of the groups X (where X=H, F, Cl, Br, I, Me, Et, *i*Pr and CF_3) should

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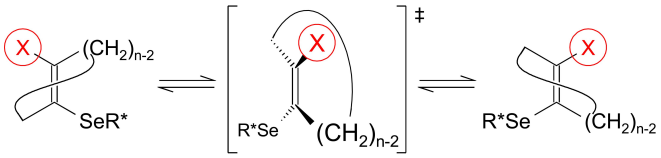


Scheme 1. Idea for the investigation.

be accessible in this way. Steric effects of substituents have already been studied, for example, on biphenyls[11] and dithiametacyclophanes.[12] However, the relation of F to H or of CF_3 to the alkyl groups (Me, Et and *i*Pr) and higher halogens was not taken into account. In modern biomedical research, compounds with substituents such as F or CF_3 are becoming increasingly important.[13,14] The question is whether there is indeed a discussed isosterism between a C–H- and C–F-group[13a] or an alkyl group (such as Et or *i*Pr) to CF_3,[15] see also ref. [16] and the recently published monography by Haupt.[17] We consider *trans*-cycloalkenes to be particularly suitable to answer this question. They have a homogeneous system of a pure carbocycle without interfering heteroatoms. The rigid region is restricted to the four planar C atoms of the CH_2–C=C–CH_2 fragment.

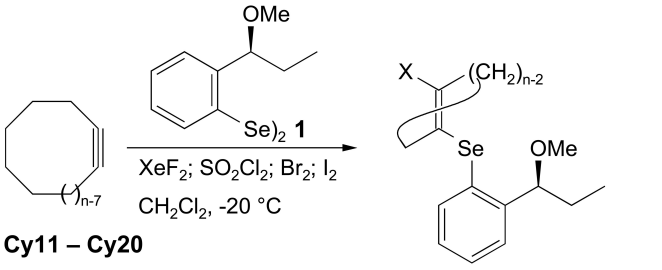
Results and Discussion

We chose (*S*)-*o*-(1-methoxypropyl)phenyldiselenide **1** as the chiral diselenide for the synthesis. It is readily prepared from (*S*)-*o*-(1-hydroxypropyl)bromobenzene with an ee value of 95%.[18] This diselenide was intended to function as a Trojan horse: On the one hand, it should enable the introduction of the halogens F to I and thus probably also the CF_3 and alkyl groups. On the other hand, it should function as a carrier of the chiral information.

The synthesis of cycloalkynes with ring sizes 9 to 20 (**Cy9**–**Cy20**) are described in the Supporting Information.

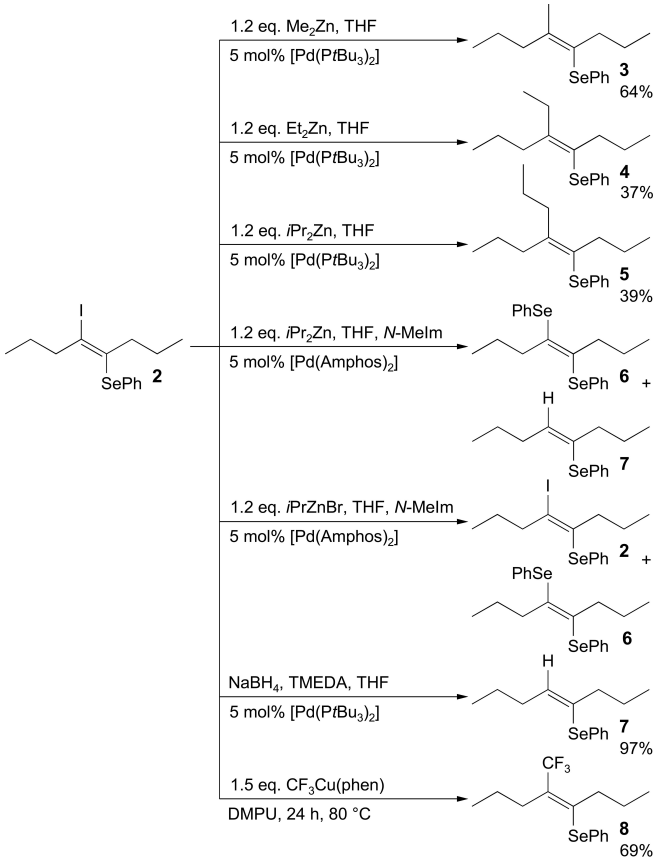
The investigation of the *trans*-cycloalkenes started with the synthesis of the fluorine compounds. Fluorinated cycloalkenes **11F**–**15F** were synthesized by fluorination of chiral diselenide **1** with XeF_2, and subsequent addition of the Ar*SeF-equivalent to the cycloalkynes **Cy11**–**Cy15** (11–15 indicates the ring size).[1a] The other halogen compounds were prepared analogously:[6] chlorides with SO_2Cl_2 (**12Cl**–**18Cl**), bromides (**15Br**–**19Br**) and iodides (**17I**–**20I**) with elemental Br_2 or I_2 (Scheme 2). Reactions to introduce Me, Et, *i*Pr and CF_3 groups into the *trans*-cycloalkenes were first tested on the model compound **2**.

Negishi coupling was chosen as the method for the often-difficult C_{sp3}–C_{sp2} coupling,[19] but see also ref. [20]. Me_2Zn and Et_2Zn couple with iodide **2** while utilizing [Pd(P*t*Bu$_3$)$_2$] as the catalyst. Both Me and Et groups (**3**, **4**) can be introduced in this way, but the latter with moderate yields (Scheme 3). Although iPr_2Zn also reacts with **2** under the same conditions, isomerization occurs. Hence, the *n*-propyl compound **5** is obtained. Recently [Pd(Amphos)$_2$] (with Amphos = *t*Bu$_2$P(*p*C$_6$H$_4$–NMe$_2$)) was reported to catalyze couplings of *sec*-alkylzinc reagents in



11F – 15F 36–63%
12Cl – 18Cl 66–92%
15Br – 19Br 73–99%
17I – 20I 78–95%

Scheme 2. Synthesis of *trans*-cycloalkenes with X=F, Cl, Br and I.



Scheme 3. Negishi couplings and trifluoromethylations with **2**.

the presence of N-methylimidazole without isomerization to the *n*-alkyl moiety.[21] Unfortunately, this catalyst does not lead to the desired result here either. **2** reacts with iPr_2Zn to form a mixture of diselenoolefin **6** and the H-compound **7**. When *i*PrZnBr is used, only diselenoolefin **6** can be detected after 24 h in addition to a large amount of starting material **2** (^{77}Se NMR and GC-MS-analysis, Figures S1 and S2 in the Supporting Information). Hence, the C–Se bond is also attacked here.

The introduction of the CF_3 group into **2** works surprisingly well with the CF_3Cu-phenanthroline complex CF_3Cu(phen). The

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use of the highly polar solvent dimethylpropyleneurea (DMPU) at 80 °C and 24 h reaction time is advantageous for such trifluoromethylations.[22]

In contrast, the use of DMF 24 h at 50 °C[23] does not lead to complete conversion of the iodide.

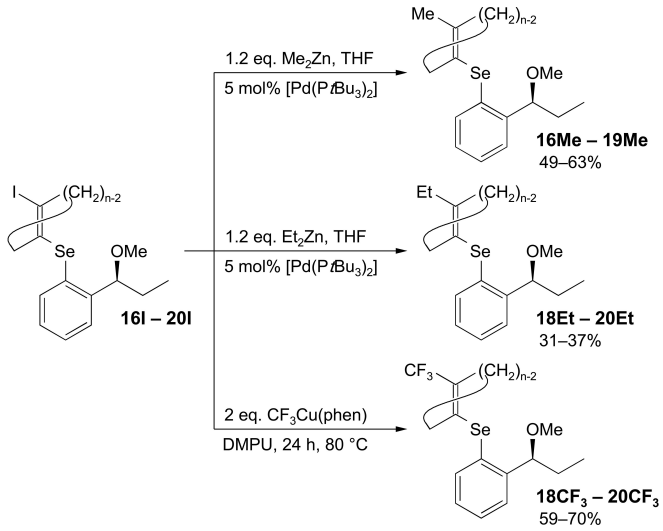
These attempts were successfully extended to the macrocyclic compounds, and the methyl (**16Me**–**19Me**) and ethyl compounds (**18Et**–**20Et**) were synthesized as well, but the latter with low purity. The syntheses of the CF_3-substituted rings **18CF$_3$**–**20CF$_3$** were successful from the iodides **18I**–**20I** and 2 equivalents of CF_3Cu(phen). The conversion was not complete when only 1.5 equivalents were used (Scheme 4). The investigation of the basic compounds with X=H is indispensable. X=H is needed as a reference for quantitative comparison of the groups X. Possible synthetic routes were again sought with the iodide **2**. A metalation of **2** with *t*BuLi or *i*PrMgCl·LiCl in THF at −100 °C gave only elimination products after hydrolysis. A catalytic hydrodeiodination with Bu_3SnH/[Pd(PPh$_3$)$_4$][24] in THF or benzene is unsuccessful, and no reduction occurs with Bu_3SnH/[Pd(P*t*Bu$_3$)$_2$]. If Et_3SiH/[Pd(P*t*Bu$_3$)$_2$] is used in THF, the iodine compound is completely converted. The formed Et_3SiI reacts with THF to give triethylsilyloxybutyl iodide.[25] However, Et_3SiI could also attack the MeOCHEt group in the ring compounds. Hydrodeiodination does not occur with Et_3N/HCO_2H in *i*PrOH or DMF and Pd-carbon[26] either. Finally, the reagents $NaBH_4$/TMEDA/[PdCl$_2$(PPh$_3$)$_2$][27] and $NaBH_4$/TMEDA/[Pd(P*t*Bu$_3$)$_2$] gave 4-phenylselenooctene **7** in 97 % yield. However, the application to iodoselenocycles is unsatisfactory. Low yields are obtained and the products are too impure for an NMR study.

A new method for *trans* addition of HI to alkynes using the reagent $PPh_3/I_2/H_2O$ was useful.[28] We were able to transfer this method to cycloalkynes with ring sizes 9 to 13 Thereby we have prepared the iodocycloalkenes **9HI**–**13HI**. Lithiation of these vinyl iodides with *t*BuLi and subsequent treatment with the chiral diselenide **1** provide the desired arylselenocycloalkenes **9H**–**13H** in high purity (Scheme 5).

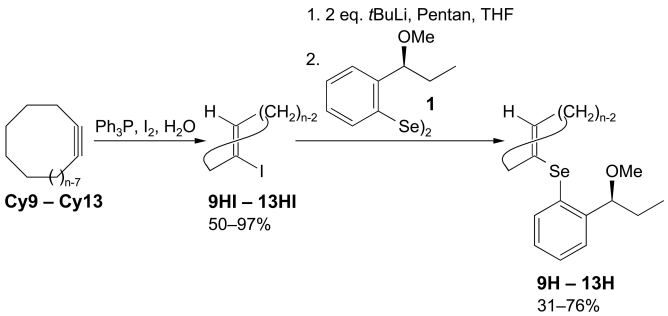
The dynamic behavior of the *trans*-cycloalkenes with Ar*Se group and X=H, F, Cl, Br, I, Me, Et and CF_3 was determined using line-shape analysis.[29] The analysis was carried out on the ^{13}C NMR spectra in the range of line broadening below the respective coalescence temperature T_C. The temperature-dependent measurements were carried out within the temperature range from −110 to 140 °C. Table S2 in the Supporting Information summarizes the *trans*-cycloalkenes analyzed by ^{13}C NMR spectroscopy and the coalescence temperatures found. The ^{13}C signals of the investigated compounds measured and analyzed at variable temperature are shown in Figures S3–S96 in the Supporting Information.

No coalescence was found at high temperatures for compounds **11F**, **12Cl**–**14Cl**, **15Br**, **16Br** and **17I**. In the case of **16Br** and **17I**, decomposition even begins. In contrast, no signal splitting was achieved at low temperatures for **13H**, **19Me** and **19Br** (Table S2 in the SI). Four compounds were completely measured for the H, F and Cl series, three for the Me, I, Et and CF_3 series and two for the Br series.

The evaluation of the data provides the Gibbs energy of activation $\Delta G^{\neq}_C$ of the investigated epimerization just below the coalescence temperature T_C. Diastereomers (usually) have different energies. Therefore, slightly different $\Delta G^{\neq}_C$ values result for both directions of inversion of the *trans*-cycloalkenes (Table 1). For the graph in Figure 1 the values for the inversion process



Scheme 4. Synthesis of *trans*-cycloalkenes with X=Me, Et and CF_3.



Scheme 5. HI addition to cycloalkynes to give iodides **9HI**–**13HI**, and synthesis of *trans*-cycloalkenes **9H**–**13H**.

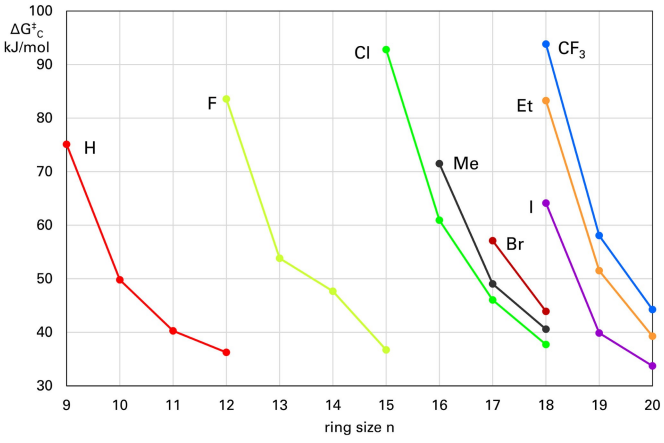


Figure 1. Gibbs energies of activation $\Delta G^{\neq}_C$ [kJ/mol] of the epimerization of *trans*-cycloalkenes with X=H, F, Cl, Br, I, Me, Et, CF_3 in dependency on the ring sizes, n = 9–20.

Table 1. Gibbs energies of activation $\Delta G^{\neq}_{C}$ [kJ/mol] of the epimerization of *trans*-cycloalkenes with X=H, F, Cl, Br, I, Me, Et, CF_3 with ring sizes n = 9–20.

n \ X	H	F	Cl	Me	Br	I	Et	CF_3
9	75.1 74.1							
10	49.8 48.6							
11	40.3 39.3							
12	36.2 35.7	83.6 82.5						
13		53.8 52.8						
14		47.7 46.0						
15		36.7 35.1	92.8 92.0					
16			60.9 59.7	71.5 70.4				
17			46.0 44.7	49.0 48.1	57.1 55.9			
18			37.7 36.4	40.6 39.2	43.9 42.6	64.1 63.3	83.3 82.4	93.8 92.8
19						39.9 38.7	51.5 50.2	58.1 57.3
20						33.7 32.3	39.3 37.6	44.2 43.3

with the slightly higher barrier are used. The error of $\Delta G^{\neq}_{C}$ can be assumed to be ± 0.5 kJ/mol.[30]

The data do not allow to decide whether the diastereomer with (*R*) or (*S*) configuration of the *trans*-cycloalkene ring is lower in energy.

For the H compounds **9H**–**12H**, $\Delta G^{\neq}_{C}$ decreases from 75 to 36 kJ/mol. **9H** shows split NMR signals at room temperature, although *trans*-cyclononene already racemize at this temperature.[7d] **10H**, even more so **11H** and **12H** as well as *trans*-cyclodecene[7d] invert rapidly at this temperature.

The F compounds **12F**–**15F** show a similar trend for the $\Delta G^{\neq}_{C}$ values as in the H compounds, only with three additional CH_2 groups in the ring. This big difference is unexpected and very surprising. The F→Cl transition also requires three additional CH_2 groups in the ring to reach similar $\Delta G^{\neq}_{C}$ values with a similar trend. This reveals an increasing demand for space. The differences in the T_C values for the same ring size, i.e. for **12H**→**12F**, **15F**→**15Cl** and **18Cl**→**18CF$_3$**, cover the entire usable temperature range of 250 K (Table S2 in the Supporting Information).

The increase in size of X in the Cl→Br and Br→I transition requires only one additional CH_2 group in the ring. The Me group is smaller than Br, it ranks between Cl and Br, see also ref. [12]. The Et group is significantly bulkier than I. The Me→Et transition requires two additional CH_2 groups in the ring. The CF_3 group is the sterically most demanding of the substituents investigated. For the compounds with ring size 18, the size steps of X in the series from Cl to CF_3 can be seen directly. Unfortunately, a precise experimental classification of the *i*Pr group is not possible here. Its size is certainly above Et but probably below CF_3, as suggested by a comparison of the steric substituent parameters according to Taft (Et 1.31, *i*Pr 1.71, CF_3 2.4, *t*Bu 2.78),[31] see also ref. [15b]. Arranged according to the steric size of the groups X examined here, the series H ≪ F ≪ Cl < Me < Br < I < Et < CF_3 results. The results show that the steric demand of a C–F group is significantly larger than that of a C–H group. Henceforth there can no longer be the notion of an almost equal steric size of both groups.

Group X of the planar X–C=C–SeR*-unit rotates through the "CH_2 handle" without any appreciable influence from the R*Se moiety. This is shown by the very similar $\Delta G^{\neq}_{C}$ values of the bromides with ring size 17 additionally prepared with (+)-neomenthyl-,[32] (+)-camphor-[33] and (*S*)-*sec*-butyldiselenide[34] (Figure 2).

The steric effect of the groups X depends on how much X interacts with the CH_2 groups of the cycle in transition state of the epimerization. This can be quantified by how far X extends into the ring, and the thickness of X itself. X is given by the C–X bond length (d_{C-X}), and the size of X by its van der Waals radius (r_{vdW}). These two values are combined to the size *S* of X, $S = d_{C-X} + r_{vdW}$. S is in good quantitative agreement with the found dependence of $\Delta G^{\neq}_{C}$- values of X (Table 2). The polyatomic

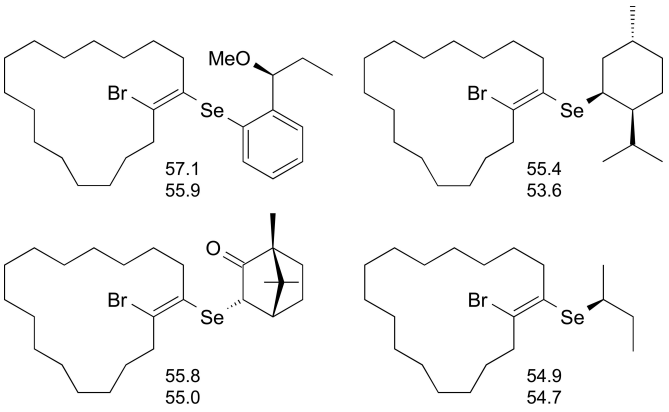


Figure 2. Gibbs energies of activation $\Delta G^{\neq}_{C}$ [kJ/mol] for the ring inversion of *trans*-bromocycloheptadecenes with different chiral groups at the selenium atom at −10 °C.

Table 2. Experimental bond distances d_{C-X} for C=C–X fragments (C–C and C–H distances for Me and Et, C–C and C–F distances for for CF_3), van der Waals radii for X (H for Me and Et, F for CF_3), and the quantity $S = d_{C-X} + r_{vdW}$ [Å].

X	d_{C-X}	r_{vdW}	S
H	0.946	1.2	2.146
F	1.369	1.47	2.839
Cl	1.747	1.75	3.497
Br	1.922	1.85	3.772
I	2.138	1.98	4.118
Me	1.499 + 0.95	1.2	3.649
Et	1.505 + 1.455 + 0.95 (2.869)	1.2	5.11 (4.069)
CF_3	1.50 + 1.332	1.47	4.302

groups are characterized by the C–C and C–H bond lengths, and the r_{vdW} for H (Me, Et). In case of CF_3, the C–C and C–F bond lengths combined with r_{vdW} of F (CF_3) is utilized. Only for the bent Et group is the value with 5.11 Å too large. The sum of the C···H distance = $\underline{C}$-CH_2–$C\underline{H_3}$ and the r_{vdW} of H, *i.e.* 4.069 Å, seems more realistic here. The experimental C–X bond lengths are mean values from compounds with C=C–X fragments (see references to Table S3 in the Supporting Information). For the van der Waals radii, the values according to Bondi[35] were used. The plot in Figure 3 shows the increase in $\Delta G^{\ddagger}_C$ with increasing values of S. The slopes for the 12- (X=H, F), 15- (X=F, Cl) and 18-membered rings (X=Cl, Me, Br, I, Et, CF_3) are 68, 85 and 71 kJ/mol per Å increase in size of X. Thus, the sensitivity of the $\Delta G^{\ddagger}_C$ values with increasing substituent size S is almost independent of the ring size. Due to this, for F we exclude a significant specific electronic C–F···CH_2 interaction in addition to the steric effect according to the measurement of S. If it would exist, the slopes for the 12- and 15-memberd rings (compounds with X=H, F, and X=F, Cl) in Figure 3 should be significantly different in comparison to the observed slope for the 18-memberd rings (compounds without X=F). However, this is not the case.

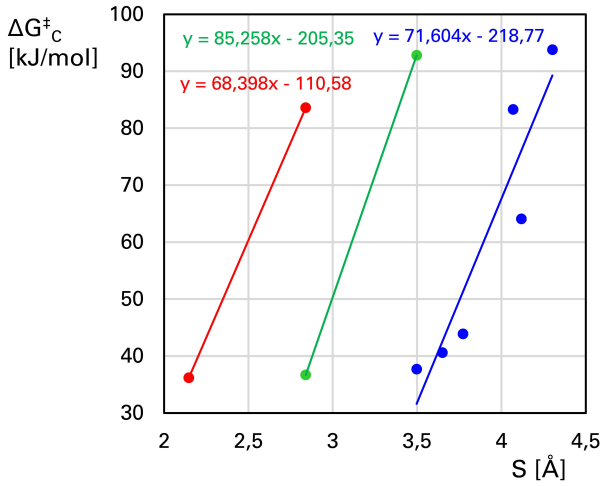


Figure 3. Dependence of the Gibbs energy of activation $\Delta G^{\ddagger}_C$ on the quantity $S = d_{C-X} + r_{vdW}$ of the groups X for ring sizes 12 (X=H, F, red), 15 (X=F, Cl, green) and 18 (X=Cl, Me, Br, I, Et, CF_3, blue).

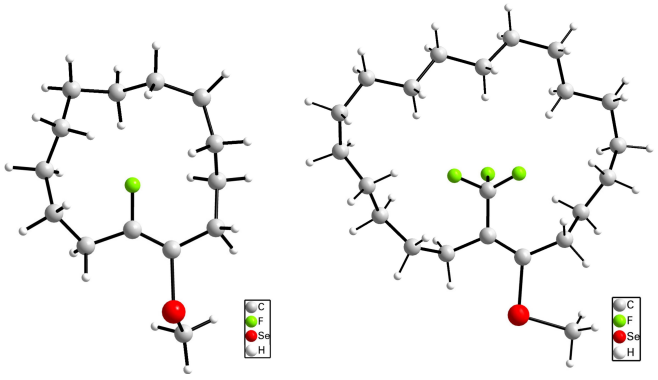


Figure 4. Calculated transition states in the enantiomerization of the *trans*-cycloalkenes for the model compounds **13FSeMe** and **20CF_3SeMe**. Theory level B3PW91/6-311 + G(d,p), basis set Se: SDB-aug-cc-pVTZ.

Additionally, we characterized the ring inversion with density functional theory. The transition state structures for the model compounds with MeSe group were calculated at the B3PW91/6-311 + G(d,p) (with SDB-aug-cc-pVTZ basis set for Se, Br, I, and corresponding ECP) level of theory.

The nature of the transition states has been verified through computation of vibrational frequencies. Each of them shows one imaginary mode that corresponds to motion of X through the ring. The transition state structures calculated for **8HSeMe–11HSeMe**, **11FSeMe–14FSeMe**, **14ClSeMe–16ClSeMe**, **16MeSeMe**, **16BrSeMe–17BrSeMe**, **17ISeMe–18ISeMe**, **18EtSeMe–20EtSeMe** and **18CF_3SeMe–20CF_3SeMe** are given in Table S4, and their atomic coordinates in Table S5 in the Supporting Information. The transition state structures of **13FSeMe** and **20CF_3SeMe** are shown in Figure 4. The structure plotted from the coordinate files with the crystal structure program DIAMOND.[36] This program was also used to determine the atomic distances for Table S4. Here the shortest X···C and X···H distances are listed in relation to the sum of the respective van der Waals radii. In the small rings of size 8–10, the H atoms of the CH_2 groups point outwards. Thus, there are almost only H_X···C repulsions. From ring size 11 onwards, the H atoms of the CH_2 groups are increasingly directed into the ring. From ring size 15 onwards, entire CH_2 groups protrude into the cavity. In addition to the X···C interactions, X···H interactions then increasingly come into play. Approximately the sum of the respective van der Waals radii gives the distance with almost no repulsion. The shorter X···C and X···H distances than the ideal distance, the greater the repulsion. An additional comparison with the experimental results shows how far below the van der Waals radii the distances must be for configurationally stable compounds exist. Furthermore, it shows when a fast ring inversion occurs, i.e. at room temperature and below. For example, the H_x···C distances are 0.8–1.03 Å shorter than the van der Waals radii for the configurationally stable 8-membered ring. For the slowly inverting 9-membered ring (T_c: 55 °C) the distances are shorter by 0.58–0.97 Å, while for the rapidly inverting 10-membered ring (T_c: −50 °C) it is only 0.39–0.78 Å and for the 11-membered ring (T_c: −85 °C) 0.34–0.54 Å. For the fluorine compounds, the F···C distances are below the van der Waals radii for the non-inverting 11-membered ring by 0.67–0.74 Å, for the very slowly inverting 12-membered ring (T_c: 87 °C) by 0.51–0.65 Å, while they decrease to 0.26–0.5 Å for the rapidly inverting 13-membered ring (T_c: −35 °C).

Conclusions

Summarizing the results, this study reported the synthesis of *trans*-cycloalkenes with the X–C=C–SeR*-unit, with a chiral group R* attached to the selenium atom. The groups X=H, F, Cl, Br, I, Me, Et and CF_3, and ring sizes 9 to 20 were utilized. The epimerization of the *trans*-cycloalkenes, *i.e.* the rotation of the group X through the cavity of the ring, can be observed by NMR spectroscopy. The chiral group R* gives rise to two diastereomers. The Gibbs energy of activation for this process was determined by temperature-dependent ^{13}C NMR measure-

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ments. The X groups exert a very strong steric effect on this ring inversion. These *trans*-cycloalkenes therefore turn out to be highly sensitive probes for characterizing the steric bulk of these groups.

Experimental Section

General

Dried solvents and argon as protective gas were used. ^{13}C, ^{19}F and ^{77}Se NMR spectra were recorded, unless otherwise noted, with a JEOL ECZ 400R or JEOL ECS 400 spectrometer at room temperature. Chemical shifts δ are reported in ppm relative to Me_4Si (^{13}C), $CFCl_3$ (^{19}F) and Me_2Se (^{77}Se). Variable temperature NMR measurements were performed on BRUKER AVANCE 300 MHz, BRUKER AVANCE 500 MHz or BRUKER AVANCE III 600 MHz spectrometers. In some cases, the number of given ^{13}C NMR signals do not agree with the theoretically expected one. The reason is mostly an overlap of two (or more) signals which could not to be separated.

For calculating kinetic data the D NMR module implemented within the BRUKER TopSpin Software (Version 3.2.1) was used.

The mass spectra were measured with a HR-EI-MS (Autospec Premier, Waters Co., Milford, MA, USA) using 80 eV electron energy and internal calibration utilizing PFK.

Quantum chemical calculations

Calculations were performed with Gaussian 09[37] (Keyword Opt = QST3) and TURBOMOLE V7.0.1 2015[38] on high-performance computer system SOROBAN at Zedat, Freie Universität Berlin (http://www.zedat.fu-berlin.de/HPC/Soroban). Basis sets 6–311 + G-(d,p) for H, C, F and Cl are implemented in Gaussian 09. Basis set SDB-aug-cc-pVTZ for Se, Br and I (and corresponding ECP) was taken from the database EMSL Basis Set Exchange Library (http://www.basissetexchange.org).

Synthesis of fluorocycloalkenes 11F–15F. Anhydrous CH_2Cl_2 (10 mL) was added by condensation to (*S*)-*o*-(1-methoxypropyl)phenyldiselenide **1** (456 mg, 1 mmol) in a vacuum apparatus at −196 °C. Then XeF_2 (169 mg, 1 mmol) was added under Ar at −25 °C and stirred at this temperature for 20 min. Thereafter, 2 mmol of the cycloalkyne **Cy11** (300 mg), **Cy12** (329 mg), **Cy13** (356 mg), **Cy14** (385 mg) or **Cy15** (413 mg) were added, stirred at −25 °C for 1 h and, additionally, at room temperature for 2 h. The solvent was removed in vacuo and the crude product was purified by column chromatography on silica gel.

If unreacted diselenide was present in these or other syntheses, it was removed as follows. The reaction mixture was taken up in 150 mL of ether. Then 30 mL H_2O were added and mixed under Ar in a separating funnel with a mixture of 500 mg $NaBH_4$ in 20 mL EtOH and shaken intensively. The ether phase was separated and shaken again with 500 mg $NaBH_4$ in 20 mL EtOH and 30 mL H_2O. The organic phase was washed with H_2O (50 mL), dried over $MgSO_4$ and the ether then removed in vacuo.

Synthesis of the chlorocycloalkenes 12Cl–18Cl

Anhydrous CH_2Cl_2 (10 mL) was added by condensation to a diselenide **1** (456 mg, 1 mmol) in a vacuum apparatus at −196 °C. Then SO_2Cl_2 (135 mg, 1 mmol) was added with a syringe under Ar at −30 °C and stirred at 0 °C for 1 h. Thereafter, at −20 °C 2 mmol of the cycloalkyne **Cy12** (329 mg), **Cy13** (356 mg), **Cy14** (385 mg), **Cy15** (413 mg), **Cy16** (441 mg), **Cy17** (468 mg) or **Cy18** (497 mg) was added, stirred at −20 °C for 1 h and, additionally, at room temperature for 2 h. The solvent was removed in vacuo and the crude product was purified by column chromatography on silica gel.

Synthesis of the bromocycloalkenes 15Br–19Br

Anhydrous CH_2Cl_2 (10 mL) was added by condensation to a diselenide **1** (456 mg, 1 mmol) in a vacuum apparatus at −196 °C. Then Br_2 (1 mmol, 1 mL 1 M solution in CCl_4) was added with a syringe under Ar at −40 °C and stirred at room temperature for 1 h. Thereafter, at −30 °C 2 mmol of the cycloalkyne **Cy15** (413 mg), **Cy16** (441 mg), **Cy17** (468 mg), **Cy18** (497 mg) or **Cy19** (525 mg) was added, stirred at −30 °C for 1 h and, additionally, overnight at room temperature. The solvent was removed in vacuo and the crude product was purified by column chromatography on silica gel.

Analogously, 1 mmol of (+)-neomenthyl- (436 mg), (+)-camphor- (462 mg) and (*S*)-*sec*-butyldiselenide (272 mg) were treated with 1 mmol Br_2 and cycloalkyne **Cy17** (468 mg).

Synthesis of the iodocycloalkenes 17I–20I

Anhydrous CH_2Cl_2 (10 mL) was added by condensation to diselenide **1** (456 mg, 1 mmol) and iodine (254 mg, 1 mmol) in a vacuum apparatus at −196 °C. Then the mixture was stirred at room temperature under Ar for 30 min. Thereafter, at −30 °C 2 mmol of cycloalkyne **Cy15** (413 mg), **Cy17** (468 mg), **Cy18** (497 mg), **Cy19** (525 mg) or **Cy20** (553 mg) was added, stirred at −30 °C for 1 h and, additionally, overnight at room temperature. The solvent was removed in vacuo and the crude product was purified by column chromatography on silica gel. In addition to the $NaBH_4$ procedure for the removal of the diselenide, any I_2 that was still present was eliminated with an aqueous $Na_2S_2O_3$ solution.

Preliminary studies on Negishi couplings, hydrodeiodination and trifluoromethylation utilizing trans-4-iodo-5-(phenylseleno)-octene (2)

Synthesis of 2

Anhydrous CH_2Cl_2 (10 mL) was added by condensation to Ph_2Se_2 (1.56 g, 5 mmol) and I_2 (1.27 g, 5 mmol) in a vacuum apparatus at −196 °C. Then the mixture was stirred at room temperature under Ar for 30 min. Thereafter, 4-octyne (1.1 g, 10 mmol) was added at −30 °C and stirred at this temperature (−30 °C) for 1 h and, additionally, at room temperature overnight. After aqueous work-up and the $NaBH_4$ procedure described above, it was chromatographed on silica gel with hexane.

Negishi coupling with 2, Me_2Zn and [Pd(tBu$_3$P)$_2$] – methylation to 3 Anhydrous THF (10 mL) was added by condensation to iodide **2** (1 mmol, 393 mg) in a vacuum apparatus at −196 °C. Then, under Ar at −20 °C, the catalyst [Pd(tBu$_3$P)$_2$] (14 mg, 0.05 mmol, 5 mol%) was added. Furthermore, Me_2Zn (1.2 mmol, 1.2 mL 1 M in heptane) was added dropwise via syringe. The mixture was stirred at −20 °C for 2 h and, additionally, at room temperature overnight. After aqueous work-up, it was chromatographed utilizing a column with silica gel and hexane.

Negishi coupling with 2, Et_2Zn and [Pd(tBu$_3$P)$_2$] – ethylation to 4 Anhydrous THF (10 mL) was added by condensation to iodide **2** (1 mmol, 393 mg) in a vacuum apparatus at −196 °C. Then, under Ar at −20 °C, the catalyst [Pd(tBu$_3$P)$_2$] (0.05 mmol, 14 mg, 5 mol%)

was added. Furthermore, Et_2Zn (1.2 mmol, 1.2 mL 1 M in hexane) was added dropwise via syringe. The mixture was stirred at −20 °C for 2 h and, additionally, at room temperature overnight. After aqueous work-up, it was chromatographed utilizing a column with silica gel and hexane.

Negishi coupling with 2, *i*Pr_2Zn and [Pd(*t*$Bu_3P)_2$] – *n*–propylation to 5 Anhydrous THF (10 mL) was added by condensation to iodide **2** (1 mmol, 393 mg) in a vacuum apparatus at −196 °C. Then, under Ar at −30 °C, the catalyst [Pd(*t*$Bu_3P)_2$] (0.05 mmol, 14 mg, 5 mol%) was added. Furthermore, *i*Pr_2Zn (1.2 mmol, 1.2 mL 1 M in toluene) was added dropwise via syringe. The mixture was stirred at −30 °C for 2 h and, additionally, at room temperature overnight. After aqueous work-up, it was chromatographed utilizing a column with silica gel and hexane.

Reactions of 2 with iPr$_2$Zn and [Pd(Amphos)$_2$]

Anhydrous THF (10 mL) was added by condensation to iodide **2** (1 mmol, 393 mg) and methylimidazole (2 mmol, 164 mg) in a vacuum apparatus at −196 °C. Then, under Ar at room temperature, the catalyst [Pd(Amphos)$_2$] (0.05 mmol, 32 mg, 5 mol%) was added. Furthermore, *i*Pr_2Zn (1.2 mmol, 1.2 mL 1 M in toluene) was added dropwise via syringe. The mixture was stirred at room temperature for 24 h. After aqueous work-up, it was chromatographed utilizing a column with silica gel and hexane. Two products formed in approximately equal parts: compound **7** and diselenoolefin **6**. Only traces of the *n*-propyl compound **5** were formed, see GC-MS analysis Figure S1 in the Supporting Information.

	7	**5**	**6**
MS:	268	310	424
δ (^{77}Se):	325.3	343.6	393.8

The addition of *i*Pr_2Zn at 0 °C, 4 h reaction at 0 °C, and 20 h at room temperature changed the product ratio only insignificantly, see GC-MS analysis Figure S2 in the Supporting Information.

Reaction of 2 with iPrZnBr and [Pd(Amphos)$_2$]

The reaction of **2** in the presence of methylimidazole and [Pd(Amphos)$_2$] with *i*PrZnBr for 24 h at room temperature gave, in addition to a large amount of unreacted starting material **2**, mainly diselenoolefin **6**, only traces of **7** but no **5**.

	2	**6**	**7**
δ (^{77}Se):	410.1	394.4	325.9

Hydrodeiodination of 2 to give 4-phenylselenooctene 7

Anhydrous THF (10 mL) was added by condensation to iodide **2** (1 mmol, 393 mg) in a vacuum apparatus at −196 °C. Then, under Ar at room temperature, the catalyst [Pd(*t*$Bu_3P)_2$] (14 mg, 0.05 mmol, 5 mol%) or [$PdCl_2$(*P*$Ph_2)_2$] (35 mg, 0.05 mmol, 5 mol%) was added. Furthermore, TMEDA (4 mmol, 465 mg) and $NaBH_4$ (3 mmol, 113 mg) were added and the mixture was stirred at room temperature for 24 h. After aqueous work-up, it was chromatographed utilizing a column with silica gel and hexane.

Trifluoromethylation with 2 and CF$_3$Cu(phen)

Under Ar CF_3Cu(phen) (1.5 mmol, 469 mg) was added to a solution of iodide 2 (1 mmol, 393 mg) in 5 mL dry dimethylpropyleneurea (DMPU). The mixture was stirred at 85 °C for 24 h. Then the reaction mixture was taken up in 100 mL ether and filtered through a frit with silica gel. The solution was washed with H_2O (15 mL), diluted HCl (15 mL), aqueous $NaHCO_3$ solution (15 mL) and H_2O (20 mL) and dried over $MgSO_4$. The solution was then concentrated on a rotary evaporator and the residue was purified by column chromatography on silica gel using hexane.

Synthesis of the methylcycloalkenes 16Me–19Me

Anhydrous THF (10 mL) was added by condensation to 1.5 mmol halide **16Br** (793 mg), **17I** (885 mg), **18I** (905 mg) or **20I** (926 mg) in a vacuum apparatus at −196 °C. Then, under Ar at −20 °C, the catalyst [(*t*$Bu_3P)_2$Pd] (0.075 mmol, 21 mg, 0.5 mol%) was added. Furthermore, Me_2Zn (1.8 mmol, 1.8 mL 1 M in heptane) was added dropwise via syringe. The mixture was stirred at −20 °C for 2 h and, additionally, at room temperature overnight. The reaction mixture was treated with an aqueous solution of NH_4Cl (20 mL) and extracted 3 times with CH_2Cl_2 (50 mL). The organic phase was washed with H_2O (50 mL) and then dried over $MgSO_4$. After removing the solvent in vacuo, the crude product was purified by column chromatography on silica gel.

Synthesis of ethylcycloalkenes 18Et–20Et

Anhydrous THF (10 mL) was added by condensation to 1 mmol iodide **18I** (604 mg), **19I** (618 mg) or **20I** (632 mg) in a vacuum apparatus at −196 °C. Then, under Ar at −40 °C, the catalyst [(*t*$Bu_3P)_2$Pd] (14 mg, 0.05 mmol, 0.5 mol%) was added. Furthermore, Et_2Zn (1.2 mmol, 1.2 mL 1 M in hexane) was added dropwise via syringe. The mixture was stirred at −40 °C for 2 h and, additionally, at room temperature overnight. The reaction mixture was treated with aqueous NH_4Cl solution (20 mL) and extracted 3 times with CH_2Cl_2 (50 mL). The organic phase was washed with H_2O (50 mL) and then dried over $MgSO_4$. After removing the solvent in vacuo, the crude product was purified by column chromatography on silica gel.

Synthesis of the trifluoromethylcycloalkenes 18CF$_3$–20CF$_3$

Under Ar CF_3Cu(phen) (2 mmol, 626 mg) was added to a solution of 1 mmol of the iodide **18I** (604 mg), **19I** (618 mg) or **20I** (632 mg) in 8 mL dry dimethylpropyleneurea (DMPU). The mixture was stirred at 85 °C for 24 h. Then the reaction mixture was dissolved in 150 mL ether and filtered through a frit with silica gel. The solution was washed with H_2O (20 mL), diluted HCl (20 mL), aqueous $NaHCO_3$ solution (20 mL) and H_2O (20 mL) and then dried over $MgSO_4$. The solution was then concentrated on a rotary evaporator and the residue was purified by column chromatography on silica gel.

Synthesis of iodocycloalkenes 9HI–13HI

5 mmol of the cycloalkyne **Cy11** (751 mg), **Cy12** (821 mg) or **Cy13** (892 mg), 5 mmol Ph_3P (1.31 g), 5 mmol I_2 (1.27 g) and 5 mmol H_2O (90 mg) were dissolved in 10 mL $CHCl_3$ and stirred at room temperature for 4 h.

For the reaction with the cycloalkynes **Cy9** and **Cy10**, the reagent was generated from Ph_3P, I_2 and H_2O in 10 mL $CHCl_3$ was stirred at room temperature for 30 min. **Cy9** (611 mg) was added at −60 °C, stirred for 4 h at −60 °C and 2 h at −20 °C. **Cy10** (681 mg) was added at 0 °C, stirred for 2 h at 0 °C and, additionally, 2 h at room temperature. After the reactions, 5 mL MeOH were added, the mixture was stirred for 5 min. Then it was concentrated on a rotary evaporator, and the residue was chromatographed on a silica gel column using hexane.

Synthesis of arylselenocycloalkenes 9H–13H

Anhydrous THF (10 mL) was added by condensation to 1 mmol iodocycloalkene **9HI** (250 mg), **10HI** (264 mg), **11HI** (278 mg), **12HI** (292 mg) or **13HI** (306 mg) in a vacuum apparatus at −196 °C. Then, under Ar at −78 °C, 2.1 mmol *t*BuLi (1.1 mL 1.9 M in pentane) was added slowly and dropwise via syringe, and stirred for 30 min. Thereafter, a solution of diselenide **1** (456 mg, 1 mmol) with dry THF was added slowly and dropwise via syringe. The mixture was stirred at −78 °C for 1 h and, additionally, at room temperature for 2 h. The diselenide was removed with $NaBH_4$, see above.

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

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