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Preparation of cyclopropanone 2,2,2-trifluoroethoxy hemiacetals *via* oxyallyl cation

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Dedicated to Professor Samir Zard, with admiration for his outstanding scientific achievements.

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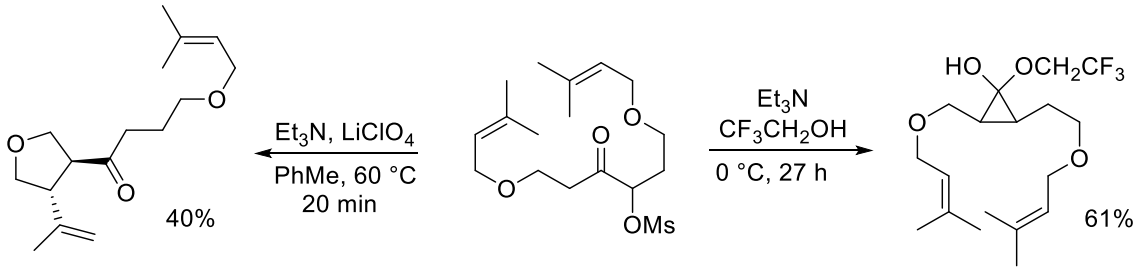
Abstract

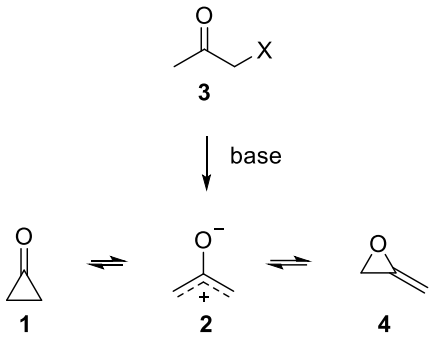
Hemiacetals of cyclopropanone can be isolated and stocked, contrary to their highly reactive parent ketone. However, they are not readily converted to cyclopropanone, which limits their use as its synthetic equivalents. 2,2.2-trifluoroethoxy hemiacetals are expected to be better cyclopropanone surrogates, however, they have never been prepared, so far. We show that oxyallyl cations with a heteroatom in the β-position can be intercepted with 2,2.2-trifluoroethanol, with formation of cyclopropanone trifluoroethoxy hemiacetals stable enough to be isolated, purified and characterized. These species can serve as synthetic equivalents of cyclopropanone under mild conditions.



Keywords: Cyclopropanone, hemiacetals, 2,2.2-trifluoroethanol, oxyallyl cation, Favorskii rearrangement.

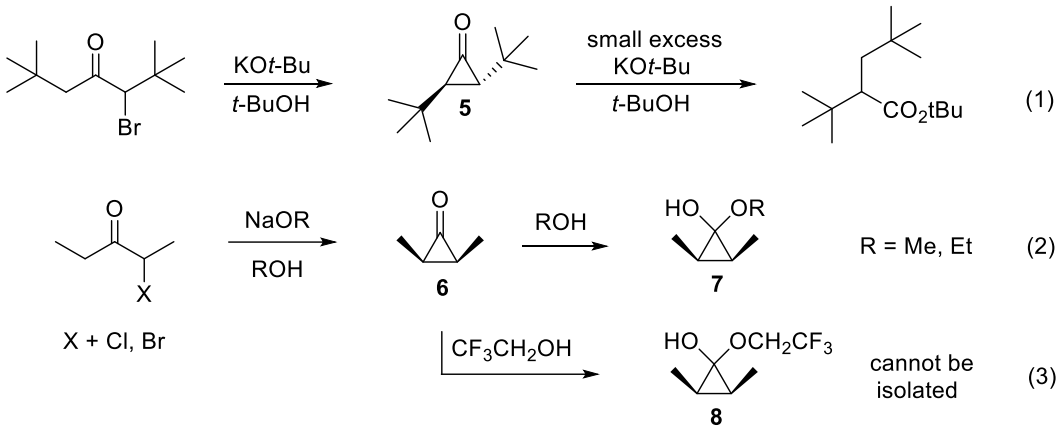
Introduction

The smallest cycloalkanone – cyclopropanone (**1**) – is a highly useful three-carbon atoms building block which, due to high ring strain, can be rearranged and implemented into various structural frameworks under mild conditions.[1,2,3] However, its extreme reactivity makes it difficult to prepare and store, hence phlegmatized synthetic equivalents are required. Due to considerable strain release, the carbonyl group of cyclopropanone is highly reactive towards nucleophiles and, in the presence of alcohols, forms relatively stable hemiacetals.[4] Unfortunately, alkoxy group is a relatively poor nucleofuge, hence the equilibrium of hemiacetals with cyclopropanone is unfavorable (for the cyclopropanone) and side reactions usually prevail. For all these reasons, it would be of interest to develop a cyclopropanone hemiacetal that would be more prone to liberate its more reactive parent ketone when needed, thus serving as a latent cyclopropanone synthon.[5,6]



Scheme 1. Tripartite equilibrium of oxyallyl cation, cyclopropanone and allene oxide

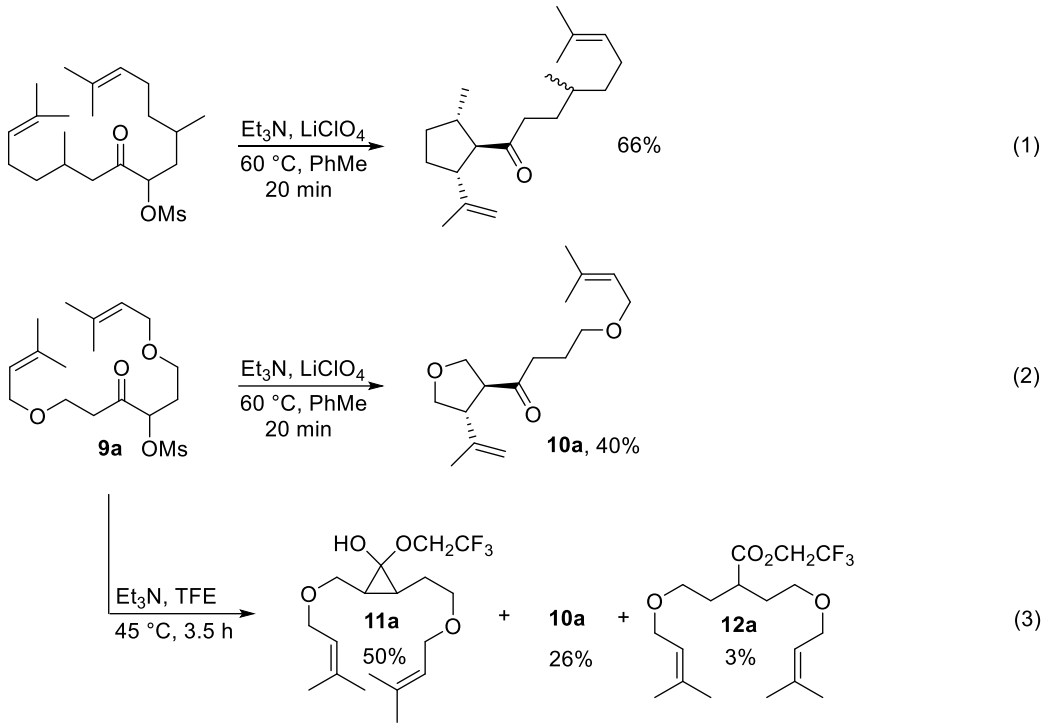
One may consider an approach to cyclopropanone via oxyallyl cation **2** (on its turn obtainable from α-haloketone **3**) which is presumed to exist in equilibrium with allene oxide **4** and cyclopropanone **1** (Scheme 1). However, this tripartite equilibrium can hardly be synthetically exploited on behalf of cyclopropanone, which is usually postulated as a transient intermediate in the Favorskii rearrangement.[7,8] Examples of cyclopropanone formation from oxyallyl cation precursors are scarce: thus, sterically extremely hindered 2,3-di-*tert*-butyl cyclopropanone **5** is persistent enough to be isolated under carefully controlled conditions (Scheme 2, example 1).[9] Less substituted cyclopropanones (e. g., **6**), too unstable to be isolated, can be intercepted (quenched) by alcohols and converted into hemiacetals (**7**).[10] This protocol work well with *e. g*., methanol and ethanol, but not with 2,2.2-trifluoroethanol (TFE), as the corresponding hemiacetal **8** quickly decomposes (Scheme 2, examples 2 and 3).



Scheme 2. Formation of cyclopropanones and cyclopropanone hemiacetals from α-halo ketones

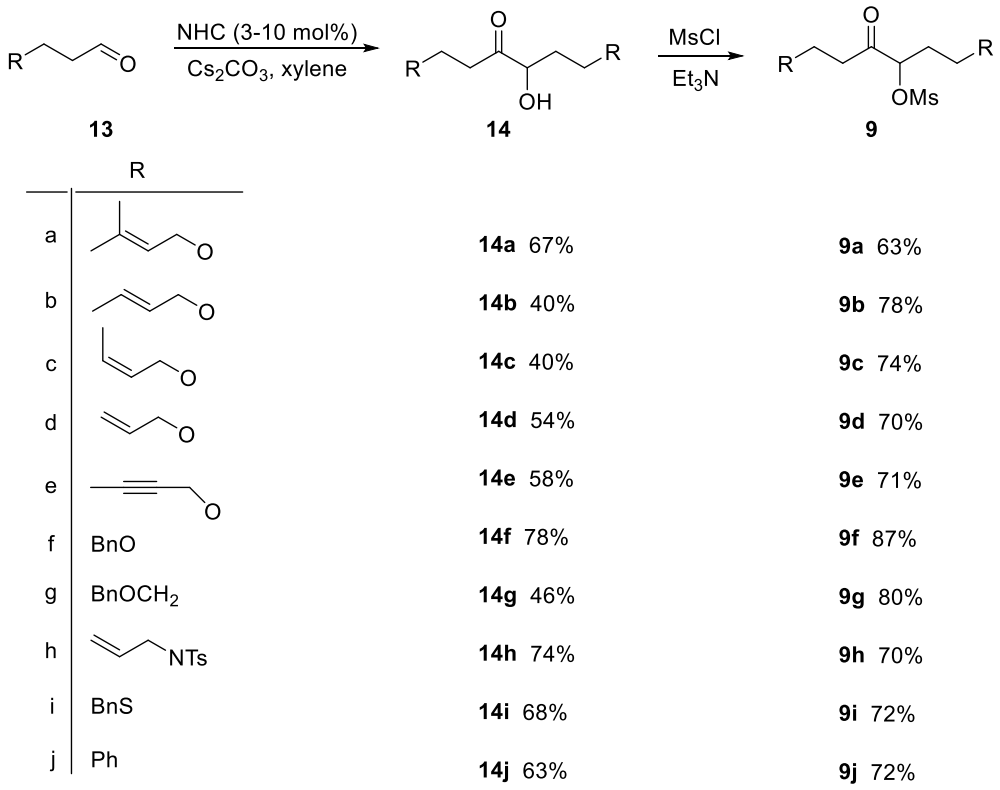
Results and Discussion

Some time ago, we developed a new method for cyclopentane ring formation, based on the intramolecular carbon-carbon bond formation of an unsaturated oxyallyl cation (Scheme 3, example 1).[11] Aiming to extend the scope of the reaction to the synthesis of heterocycles, we submitted compound **9a** to the previously developed cyclization conditions (Scheme 3, example 2). When the reaction was performed in toluene, or dichloromethane, only the expected THF-derivative **10a** was obtained; however, in TFE as solvent a mixture of products was obtained with the major one identified as cyclopropanone trifluoroethoxy hemiacetal **11a** (example 3). The other reaction products were THF derivative **10a** and the product of the Favorskii rearrangement **12a**. Lowering the reaction temperature to 0 °C allowed us to isolate compound **11a** in 61% yield. Literature search revealed only one example of such cyclopropanone trifluoroethoxy hemiacetal, which could not be isolated, but was detected in a product mixture by GC/MS.[10] This result prompted us to further explore the reaction and its preparative potential.



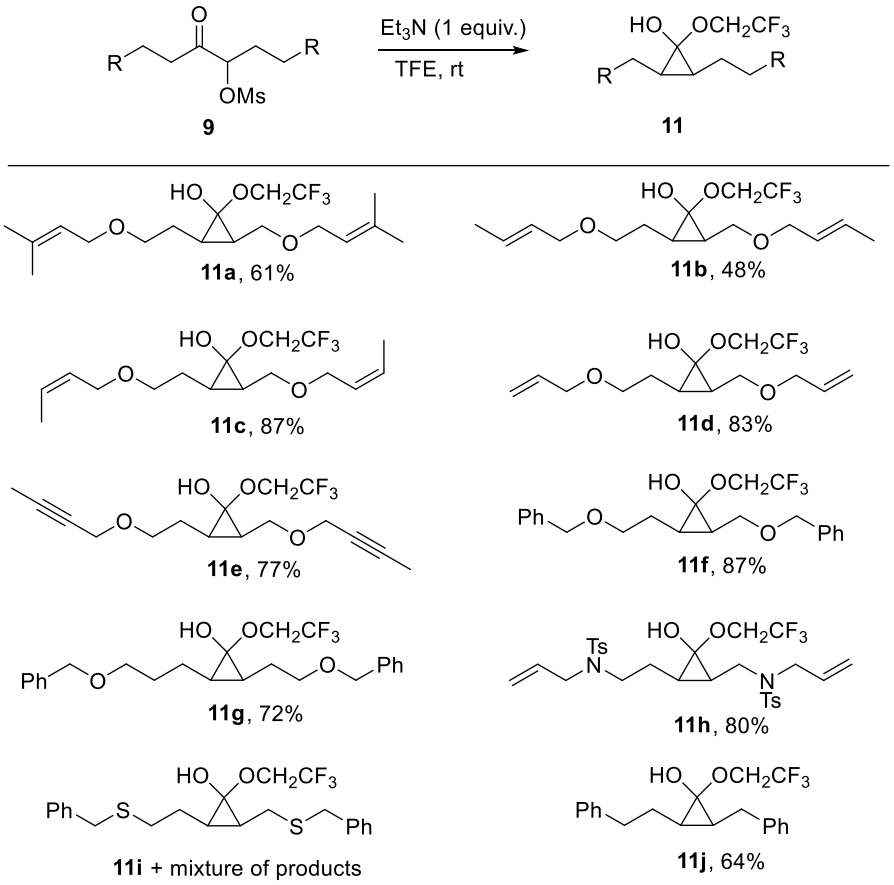
Scheme 3. Cyclizations of oxyallyl cation

The oxyallyl cation (from **9a**) that gave cyclopropanone hemiacetal **11a** possesses an oxygen atom in β-position (with respect to the carbonyl of the precursor). To examine whether this structural feature may determine the course of the reaction, we synthesized a number of structural analogues with oxygen, as well as with other heteroatoms in the β-position. These compounds were synthesized by NHC-catalyzed benzoin condensation of the suitable aldehyde precursors **13**,[12] followed by conversion of acyloins **14** into the corresponding mesylates **15** – oxyallyl cation precursors – as shown in Scheme 4.[13]



Scheme 4. Synthesis of precursors

Upon exposure to triethylamine and TFE at room temperature, all compounds with oxygen atom in β-position (**9a**-**f**) afforded cyclopropanone trifluoroethoxy hemiacetals **11a**-**f** in moderate to excellent yields (Scheme 5). The substrate **9g** with alkoxy group in γ-position also gave cyclopropanone hemiacetal **11g** in good yield.



Scheme 5. Preparation of cyclopropanone 2,2.2-trifluoroethoxy hemiacetals

Substituting nitrogen for oxygen in the side-chain (**9h**), also resulted in the formation of the corresponding cyclopropanone hemiacetal **11h** in high yield. However, sulfur-containing precursor **9i** gave a mixture of products, where the desired hemiacetal **11i** predominated, but could not be isolated pure enough to be properly characterized. Somewhat surprisingly, β-phenyl precursor **9j** (without heteroatoms) also produced cyclopropanone hemiacetal **11j**. All cyclopropanone hemiacetals were obtained as single diastereoisomers; however, we are not able to unambiguously assign stereochemistry to the products as, according to NOESY correlations, not all products are of the same relative configuration. Thus, NOESY data for compound **11d** indicate *trans*-configuration of allyloxymethyl and hydroxyl substituents, whereas 2-allyloxyethyl group is in *cis*-position (Figure 1). On the contrary, NOESY data for compound **11h** indicate *cis*-configurations of both carbon substituents, relative to the hydroxyl group.

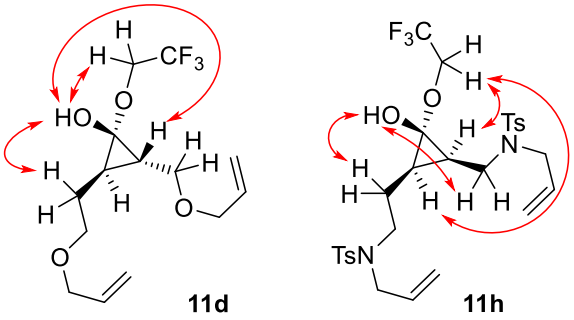
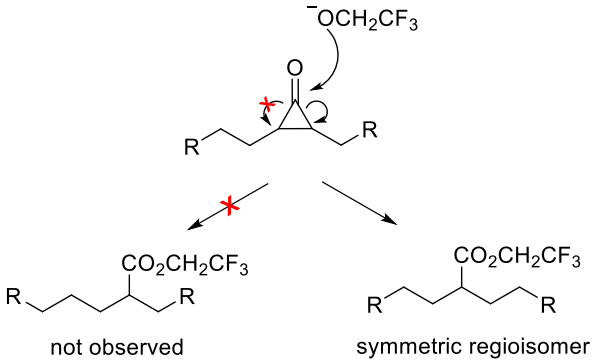


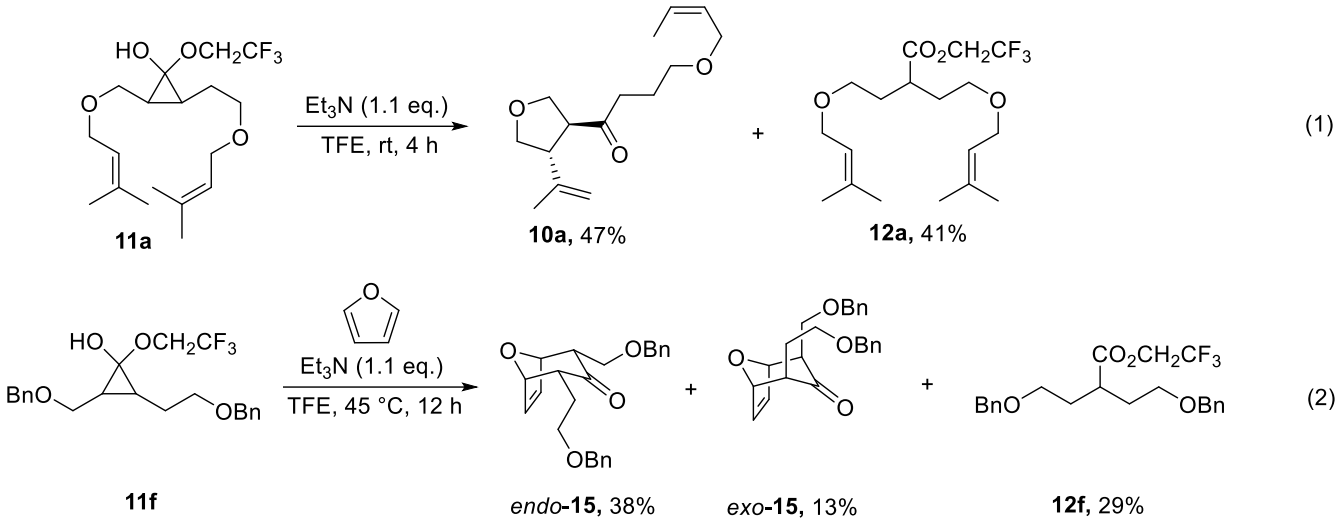
Figure 1. NOESY correlations of cyclopropanone 2,2.2-trifluoroethoxy hemiacetals

Attempts to prepare crystalline derivative for X-ray crystallographic structure determination were not successful, due to instability of products (whereas stable enough to be isolated, purified and characterized, they decompose quickly even at –20 °C). Occasionally, small amounts of the Favorskii rearrangement products were observed. The Favorskii rearrangement occurred with complete regioselectivity, giving the symmetric regioisomers exclusively (Scheme 6). This is an interesting finding, in light of the previous study where mixtures of regioisomers were obtained even with large steric differences of substituents on cyclopropanone.[14]



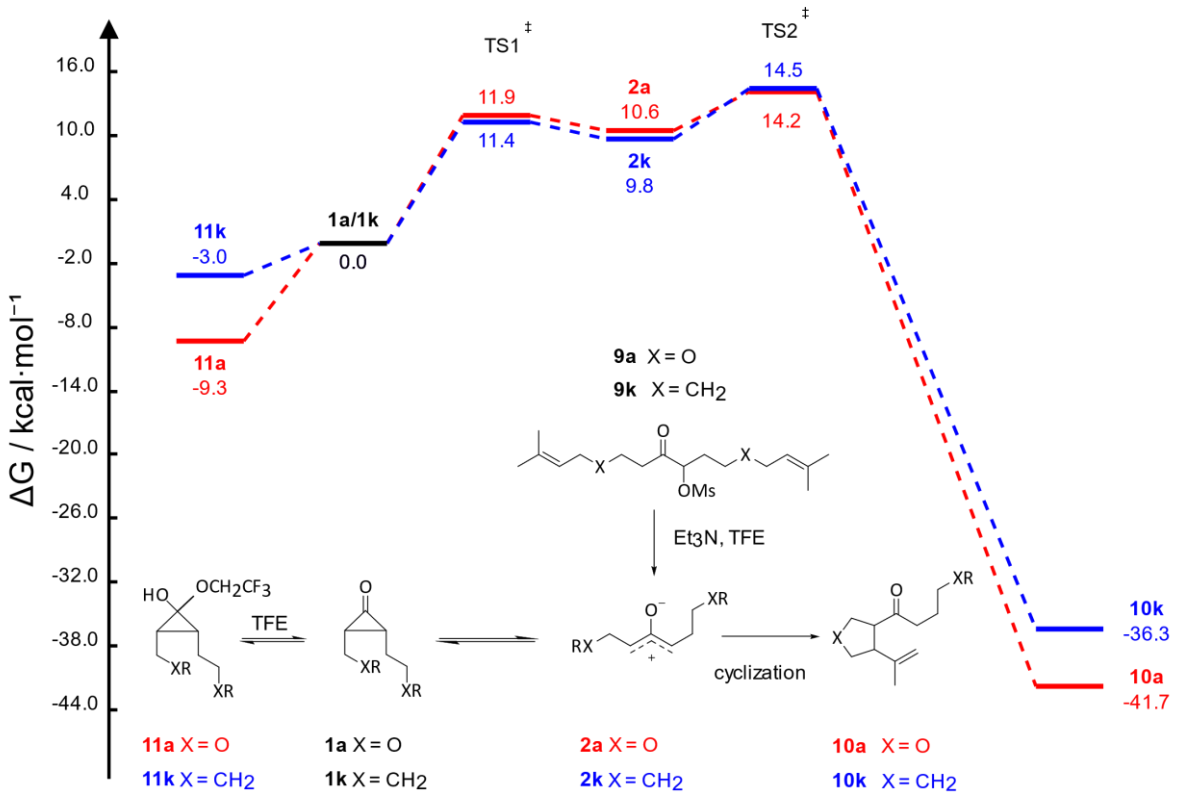
Scheme 6. Regioselective Favorskii rearrangement

Contrary to other, *e.g.*, methyl, or ethyl, cyclopropanone hemiacetals (which require two weeks for conversion to the parent ketone),[15] trifluoroethoxy hemiacetals rearrange within hours at room temperature. Thus, after 4 h at room temperature, hemiacetal **11a** is completely converted into a 1:1 mixture of THF derivative **10a** and the Favorskii product **12a**, in 88% combined yield (Scheme 7, example 1). Hemiacetals **11d** and **11h**, which cannot cyclize, afford the products of the Favorskii rearrangement exclusively. In the presence of furan, cyclopropanone generated from hemiacetal **11f** undergoes intermolecular reaction – (4+3) cycloaddition – affording products **15** in 51% combined yield accompanied with Favorskii product **12f** (29%) (Scheme 7, example 2).



Scheme 7. Cyclopropanone 2,2.2-trifluoroethoxy hemiacetals as cyclopropanone surrogates

To clarify the mechanistic manifold of this reaction system, we performed calculations at rev-DOD-PBEP86-D4/TZP/COSMO(TFE)//B97-D/TZP/COSMO(TFE) level of theory.[16] The results are represented in Scheme 8. The reaction of α-mesyloxy ketones (**9a** and **9k**) with trimethylamine gives oxyallyl cation, which can give rise to either the thermodynamic product of type **10** (*i.e.*, cyclopentane **10k** or tetrahydrofuran **10a**) or the kinetic product **1** (*i.e.*, cyclopropanone). Both reactions occur with relatively small activation energies, whereas the activation barrier for the kinetic process is c.a. 2 – 3 kcal mol^{-1} lower than the thermodynamic one. However, cyclopropanone is an unstable species that undergoes barrierless nucleophilic addition in the presence of alcohols. Our calculations show that the TFE-hemiacetal **11a** is more stable than the all-carbon analog **11k** for 6.3 kcal mol^{-1}. The additional stability of **11a** is due to the intramolecular hydrogen bonding absent in **11k**. When the reaction is performed at room temperature, the energy barrier of 21.2 kcal mol^{-1} (from **11a** to **TS1**) is sufficient to isolate the hemiacetal **11a** as the kinetic product. It appears that 6.3 kcal mol^{-1} provided by the intramolecular hydrogen bond is decisive for the stability of the hemiacetal, as the carbon analogs cannot be isolated. However, in the absence of alcohol, the thermodynamic equilibrium is established where a much more stable cyclopentane **10k** (or tetrahydrofuran **10a**) product is exclusively obtained. As the reaction temperature increases, hemiacetal **11a** can undergo a reverse reaction to oxyallyl cation, which then undergoes cyclization, or other reactions (such as 4+3 cycloaddition). We believe that a similar explanation holds for the nitrogen analog **11h**. However, at present, we don't have an answer for the unexpected stability of all-carbon analog **11j**.



Scheme 8. Gibbs free energy profile of the reaction system, calculated at rev-DOD-PBEP86-D4/TZP/COSMO(TFE)//B97-D/TZP/COSMO(TFE) level of theory (at 298.15 K, in kcal mol^{-1} relative to cyclopropanone **1a**/**1k**).

Conclusions

To summarize, we prepared, for the first time, cyclopropanone trifluoroethoxy hemiacetals, by funneling the oxyallyl cation/cyclopropanone/allene oxide tripartite equilibrium into a single product via the addition of trifluoroethanol. Calculations indicate that the reaction outcome is controlled by a fine balance of kinetic and thermodynamic effects, where the intramolecular hydrogen bond stabilizes the hemiacetals. The trifluoroethoxy hemiacetals can be used as latent cyclopropanone synthons, as they undergo the reverse reaction (*i.e.*, elimination of trifluoroethanol) much easier than the ordinary alkoxy analogues. All products were obtained as single diastereoisomers, but the determination of configuration was hampered by instability of products, and additional efforts are needed to clarify the stereochemical issue.

Experimental Section

General. All chromatographic separations[17,18,19] were performed on Silica, 10-18, 60Å, ICN Biomedicals and Merck Silica gel 60 (0.063-0.200 mm) (70-230 mesh ASTM). Standard techniques were used for the purification of reagents and solvents.[20] Petroleum ether refers to the fraction boiling at 70–72 °C. NMR spectra were recorded on a Varian/Agilent 400, (^{1}H NMR at 400 MHz, ^{13}C NMR at 100 MHz) and on a Bruker Avance III 500 (^{1}H NMR at 500 MHz, ^{13}C NMR at 126 MHz). Chemical shifts are expressed in ppm (δ) using tetramethylsilane as internal standard, coupling constants (*J)* are in Hz. IR spectra were recorded on a Nicolet 6700 FT instrument, and are expressed in cm^{-1}. Mass spectra were obtained on Agilent technologies 6210 TOF LC/MS instrument (LC: series 1200) and LTQ Orbitrap XL hybrid FTMS (Thermo Scientific).

3-(Allyloxy)propanal (13d). IBX (1.8 g, 6.45 mmol, 1.5 eq) was added to the solution of 3-(allyloxy)propan-1-ol[21] (0.5 g, 4.3 mmol, 1.0 eq) in acetonitrile (43 mL). After stirring at 65 °C for 2 h, the reaction mixture was filtrated through Celite and distilled to afford 220.3 mg (45%) of the compound **13d**, as yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.80 (t, *J* 1.7 Hz, 1H), 5.87–5.85 (m, 1H), 5.31–5.25 (m, 1H), 5.22–5.16 (m, 1H), 4.00 (d, *J* 5.6 Hz, 2H), 3.78 (t, *J* 6.1 Hz, 2H), 2.68 (td, *J* 6.1, 1.7 Hz, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) *δ* 201.3, 134.5, 117.5, 72.3, 63.9, 44.0.

General procedure 1. Acyloin condensation.[12] A suspension of aldehyde (1 eq), anhydrous Cs_2CO_3 (0.03-0.1 eq) and *N*-heterocyclic carbene precatalyst NHC (0.03-0.1 eq) in dry xylene (0.2-1.3 M) was stirred at room temperature for 15-72 h. The reaction mixture was then quenched with distilled water and extracted with ethyl acetate. The combined organic extract was washed with brine, dried over anh. $MgSO_4$ and concentrated *in vacuo*. Column or dry flash chromatography of the residue afforded desired hydroxy ketone **14**.

4-Hydroxy-1,6-bis((3-methylbut-2-en-1-il)oksi)hexan-3-one (14a).[11] Prepared by general procedure 1, using 3-(3-methylbut-2-enyloxy)propanal[22] (417 mg, 2.93 mmol, 1 eq), NHC (106.3 mg, 0.293 mmol, 0.1 eq), cesium carbonate (57.3 mg, 0.176 mmol, 0.06 eq) and xylene (13.6 mL), at room temperature, during 24 h. Purification by dry-flash chromatography (petroleum ether/ethyl acetate = 4/1) afforded 235.7 mg (67%) of hydroxy ketone **14a**, as yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) *δ* 5.34–5.24 (m, 2H), 4.26 (dt, *J* 6.8, 4.1 Hz, 1H), 3.95 (d, *J* 6.9 Hz, 2H), 3.91–3.87 (m, 2H), 3.79 (d, *J* 4.2 Hz, 1H), 3.75–3.67 (m, 2H), 3.58–3.51 (m, 2H), 2.86 (dt, *J* 16.4, 6.1 Hz, 1H), 2.75 (dt, *J* 16.4, 6.6 Hz, 1H), 2.13–2.03 (m, 1H), 1.97–1.89 (m, 1H), 1.74 (s, 6H), 1.66 (s, 3H), 1.65 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) *δ* 210.5, 136.8, 136.5, 120.4 (2×C), 74.5, 67.1 (2×C), 65.1, 64.5, 38.1, 33.0, 25.3, 25.3, 17.6, 17.5.

1,6-Bis(allyloxy)-4-hydroxyhexan-3-one (14d). Prepared by general procedure 1, using **13d** (39.6 mg, 0.347 mmol, 1 eq), NHC (12.6 mg, 0.035 mmol, 0.1 eq), cesium carbonate (6.8 mg, 0.021 mmol, 0.06 eq) and xylene (1.6 mL), at room temperature, during 24 h. Purification by dry-flash chromatography (petroleum ether/ethyl acetate = 4/1) afforded 21.7 mg (54%) of compound **14d**, as yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.92–5.77 (m, 2H), 5.28–5.11 (m, 4H), 4.30–4.24 (m, 1H), 3.95 (d, *J* 5.6 Hz, 2H), 3.89 (d, *J* 5.6 Hz, 2H), 3.77–3.65 (m, 3H), 3.56 (t, *J* 5.7 Hz, 2H), 2.85 (dt, *J* 16.5, 6.0 Hz, 1H), 2.76 (dt, *J* 16.4, 6.6 Hz, 1H), 2.10 (dq, *J* 14.5 Hz, 4.7, 1H), 1.95 (dq, *J* 12.7 Hz, 6.3, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$) *δ* 210.8, 134.6, 134.5, 117.3, 117.1, 74.9, 72.2, 65.7, 65.3, 38.5, 33.5. **IR** (ATR) ν_{max}: 3464, 3081, 2867, 1716, 1647, 1520, 1453, 1422.

1,6-Bis(but-2-yn-1-yloxy)-4-hydroxyhexan-3-one (14e). Compound was isolated as a side product in cross-benzoin condensation of 3-(but-2-ynyloxy)propanal with benzaldehyde.[7] **^{1}H NMR** (500 MHz, $CDCl_3$) *δ* 4.27–4.22 (m, 1H), 4.08–4.03 (m, 2H), 4.01–3.97 (m, 2H), 3.81–3.71 (m, 2H), 3.69–3.64 (m, 1H), 3.64–3.54 (m, 2H), 2.84 (dt, *J* 16.7, 6.1 Hz, 1H), 2.74 (dt, *J* 16.7, 6.6 Hz, 1H), 2.09 (ddt, *J* 14.7, 6.1, 4.4 Hz, 1H), 1.95–1.85 (m, 1H),

1.83–1.79 (m, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 210.6, 82.8, 82.6, 75.0, 74.7, 65.4, 64.8, 59, 58.9, 38.3, 38.4, 3.6. **IR** (ATR) ν_{max}: 3465, 2957, 2925, 2859, 1720, 1514, 1446, 1359. **HRMS** (m/z) $[M+K]^+$ calcd. for $C_{14}H_{20}O_4$: 291.0993, found: 291.1002.

1,6-Bis(benzyloxy)-4-hydroxyhexan-3-one (14f). Prepared by general procedure 1, using 3-(benzyloxy)propanal[23] (224 mg, 1.364 mmol, 1 eq), **NHC** (15.0 mg, 0.041 mmol, 0.03 eq), cesium carbonate (13.0 mg, 0.041 mmol, 0.03 eq) and xylene (1 mL), at room temperature, during 17 h. Purification by dry-flash chromatography (petroleum ether/ethyl acetate = 7/3) afforded 175.1 mg (78%) of hydroxy ketone **14f,** as a colorless oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.37–7.26 (m, 10H), 4.47 (s, 2H), 4.42 (s, 2H), 4.31 (dd, *J* 6.0, 4.4 Hz, 1H), 3.79–3.73 (m, 1H), 3.70–3.58 (m, 3H), 2.87 (dt, *J* 16.5, 6.0 Hz, 1H), 2.81–2.73 (m, 1H), 2.17–2.10 (m, 1H), 2.06–1.96 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 210.9, 138.2, 128.6, 128.6, 128.0, 127.9, 127.9, 75.0, 73.6, 66.0, 65.5, 38.6, 33.7. **IR** (ATR) ν_{max}: 3452, 3062, 3031, 2866, 1718, 1495, 1453, 1365. **HRMS** (m/z) $[M+K]^+$ calcd. for $C_{20}H_{24}O_4$: 367.1306, found: 367.1322.

1,8-Bis(benzyloxy)-5-hydroxyoctan-4-one (14g). Prepared by general procedure 1, using 4-(benzyloxy)butanal[23] (468 mg, 2.63 mmol, 1 eq), NHC (31.2 mg, 0.086 mmol, 0.03 eq), cesium carbonate (27.7 mg, 0.085 mmol, 0.03 eq) and xylene (7 mL), at room temperature, during 72 h. Purification by dry-flash chromatography (petroleum ether/ethyl acetate = 3/1) afforded 214.2 mg (46%) of hydroxy ketone **14g**, as a colorless oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.37–7.26 (m, 10H), 4.50 (s, 2H), 4.47 (s, 2H), 4.19–4.13 (m, 1H), 3.60 (d, *J* 3.4 Hz, 1H), 3.57–3.45 (m, 4H), 2.69–2.51 (m, 2H), 2.02–1.89 (m, 2H), 1.83–1.54 (m, 4H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 212.3, 138.5, 138.4, 128.5, 127.8 (2C), 75.0, 73.6, 66.0, 65.5, 38.6, 33.7. **IR** (ATR) ν_{max}: 3452, 3062, 3031, 2866, 1718, 1495, 1453, 1365. **HRMS** (m/z) $[M+K]^+$ calcd. for $C_{22}H_{28}O_4$: 395.1619, found: 395.1620.

***N,N'*-(3-hydroxy-4-oxohexane-1,6-diyl)bis(*N*-allyl-4-methylbenzenesulfonamide) (14h).** Prepared by general procedure 1, using N-allyl-4-methyl-N-(3-oxopropyl)benzenesulfonamide[24] (91.1 mg, 0.34 mmol, 1 eq), NHC (6.2 mg, 0.017 mmol, 0.05 eq), cesium carbonate (6.4 mg, 0.020 mmol, 0.06 eq) and xylene (1.6 mL), at room temperature, during 15 h. Purification by column chromatography (petroleum ether/ethyl acetate = 1/1) afforded 67.3 mg (74%) of hydroxy ketone **14h**, as a yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.71–7.67 (m, 4H), 7.31 (d, *J* 8.0 Hz, 4H), 5.69–5.54 (m, 2H), 5.23–5.12 (m, 4H), 4,20 (ddd, *J* 8.7, 4.9, 3.5 Hz, 1H), 3.85 – 3.73 (m, 4H), 3.50 (d, *J* 5.0 Hz, 1H), 3.41–3.30 (m, 3H), 3.11 (ddd, *J* 14.4, 7.6, 4.6 Hz, 2H), 3.00–2.83 (m, 2H), 2.43 (s, 6H), 2.13 (dtd, *J* 14.0, 7.8, 3.4 Hz, 1H), 1.79 – 1.65 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 210.5, 143.7, 136.5, 133.0, 132.8, 129.9, 127.4, 127.3, 119.7, 119.5, 74.3, 51.9, 51.8, 43.8, 42.4, 38.3, 32.7, 21.7. **IR** (ATR) ν_{max}: 3505, 2925, 2734, 1724, 1644, 1598, 1494, 1451, 1340. **HRMS** (m/z) $[M+Na]^+$ calcd. for $C_{26}H_{34}N_2O_6S_2$: 557.1756, found: 557.1740.

1,6-Bis(benzylthio)-4-hydroxyhexan-3-one (14i). Prepared by general procedure 1, using 3-(benzylthio)propanal[25] (200 mg, 1.1 mmol, 1 eq), NHC (24 mg, 0.066 mmol, 0.06 eq), cesium carbonate (22 mg, 0.066 mmol, 0.06 eq) and xylene (3 mL), at room temperature, during 15 h. Purification by column chromatography (petroleum ether/ethyl acetate = 75/25) afforded 135.4 mg (68%) of hydroxy ketone **14i**, as a yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.31–7.18 (m, 10H), 4.13 (dt, *J* 8.3, 4.0 Hz, 1H), 3.70–3.66 (m, 4H), 3.31 (d, *J* 4.9 Hz, 1H), 2.79–2.42 (m, 6H), 1.92–1.82 (m, 1H), 1.67 – 1.56 (m, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 210.2, 138.5, 138.3, 129.0, 128.9, 128.7, 127.3, 127.3, 75.5, 38.1, 37.0, 36.8, 33.4, 27.4, 25.3. **IR** (ATR) ν_{max}: 3471, 3082, 3060, 3027, 2919, 1711, 1601, 1494, 1452, 1420. **HRMS** (m/z) $[M+Na]^+$ calcd. for $C_{20}H_{24}O_2S_2$: 383.1115, found: 383.1106.

4-Hydroxy-1,6-diphenylhexan-3-one (14j).[26]

Prepared by general procedure 1, using 3-phenylpropanal (150 mg, 1.12 mmol, 1 eq), NHC (40 mg, 0.112 mmol, 0.1 eq), cesium carbonate (36 mg, 0.112 mmol, 0.1 eq) and xylene (2.1 mL), at room temperature during 64 h. Purification by dry-flash chromatography (petroleum ether/ethyl acetate = 925/75) afforded 105.5 mg (63%) of hydroxy ketone **14j**, as a yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) *δ* 7.34–7.12 (m, 10H), 4.12 (dd, *J* 8.3, 3.5 Hz, 1H), 3.01–2.88 (m, 4H), 2.82–2.64 (m, 4H), 2.14–2.04 (m, 1H), 1.83–1.72 (m, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) *δ* 211.1, 177.8, 141.0, 140.4, 140.1, 128.5 (2C), 128.2 (2C), 126.3 (2C), 126.1, 75.7, 39.6, 35.4, 31.0, 30.6, 29.5.

General procedure 2. Mesylation of hydroxy ketones.[13] Mesyl chloride (1.5-2 eq) was added to a solution of hydroxy ketone 14 (1 Eq), triethylamine (2.5-3.5 eq) and DMAP (0.1 eq) in CH_2Cl_2 (0.2-0.6 M) at -30 °C. After the reaction was completed (10-30 min.), the reaction mixture was concentrated in *vacuo* and the residue was purified by column or dry flash chromatography to afford desired mesylate **9**.

1,6-Bis(allyloxy)-4-oxohexan-3-yl methanesulfonate (9d). Prepared by general procedure 2, using **14d** (21.7 mg, 0.095 mmol, 1 eq), mesyl chloride (41 µL, 0.53 mmol, 2 eq), triethylamine (40 µL, 0.285 mmol, 3 eq), DMAP (1.2 mg. 0.009 mmol, 0.1 eq) and CH_2Cl_2 (0.44 mL), during 30 minutes. Dry-flash chromatography (petroleum ether/acetone = 4/1) afforded 20.5 mg (70%) of **9d**, as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.93–5.81 (m, 2H), 5.29–5.21 (m, 2H), 5.20–5.14 (m, 3H), 3.98–3.92 (m, 4H), 3.71 (t, *J* 6.2 Hz, 2H), 3.62–3.50 (m, 2H), 3.10 (s, 3H), 2.90–2.75 (m, 2H), 2.26–2.15 (m, 1H), 2.13–2.03 (m, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) *δ* 204.6, 134.6, 134.4, 117.4, 117.3, 81.6, 72.3, 72.1, 64.9, 64.5, 39.1, 38.8, 31.7. **IR** (ATR) ν_{max}: 3082, 3017, 2870, 1730, 1646, 1518, 1479, 1420, 1359, 1249.

1,6-Bis(but-2-yn-1-yloxy)-4-oxohexan-3-yl methanesulfonate (9e). Prepared by general procedure 2, using **14e** (67.5 mg, 0.267 mmol, 1 eq), mesyl chloride (41 µL, 0.53 mmol, 2 eq), triethylamine (112 µL, 0.8 mmol, 3 eq), DMAP (3 mg. 0.027 mmol, 0.1 eq) and CH_2Cl_2 (1.4 mL), during 10 minutes. Dry-flash chromatography (petroleum ether/acetone = 6/4) afforded 62.6 mg (71%) of **9e**, as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) *δ* 5.13 (dd, *J* 8.1, 4.1 Hz, 1H), 4.10–4.06 (m, 2H), 3.78 (t, *J* 6.2 Hz, 2H), 3.66–3.59 (m, 2H), 3.12 (s, 3H), 2.86 (td, *J* 6.2, 4.2 Hz, 2H), 2.26–2.17 (m, 1H), 2.13–2.00 (m, 1H), 1.88–1.81 (m, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) *δ* 204.6, 83.2, 83.0, 81.5, 75.0, 74.9, 64.5, 64.3, 59.1, 59.0, 39.0, 38.8, 31.6, 3.8. **IR** (ATR) ν_{max}: 3435, 3024, 2923, 2243, 1728, 1360. **HRMS** (m/z) $[M+K]^+$ calcd. for $C_{15}H_{22}O_6S$: 369.0769, found: 369.0799.

1,6-Bis(benzyloxy)-4-oxohexan-3-yl methanesulfonate (9f). Prepared by general procedure 2, using **14f** (41.5 mg, 0.126 mmol, 1 eq), mesyl chloride (15 µL, 0.189 mmol, 1.5 eq), triethylamine (44 µL, 0.3 mmol, 2.5 eq), DMAP (1.5 mg. 0.0126 mmol, 0.1 eq) and CH_2Cl_2 (0.6 mL), during 10 minutes. Dry-flash chromatography (petrol ether/ethyl acetate = 7/3) afforded 44.7 mg (87%) of **9f**, as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) *δ* 7.37–7.27 (m, 10H), 5.19 (dd, *J* 7.7, 4.2 Hz, 1H), 4.46 (s, 4H), 3.71 (t, *J* 6.2 Hz, 2H), 3.66–3.56 (m, 2H), 3.03 (s, 3H), 2.90–2.76 (m, 2H), 2.27–2.18 (m, 1H), 2.16–2.05 (m, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) *δ* 204.5, 138.0, 137.9, 128.6, 128.5, 128.0, 127.9, 127.8, 81.6, 73.4, 73.4, 65.0, 64.7, 39.1, 38.7, 31.8. **IR** (ATR) ν_{max}: 3486, 3063, 3030, 2868, 1728, 1495, 1495, 1454, 1360. **HRMS** (m/z) $[M+Na]^+$ calcd. for $C_{21}H_{26}O_6S$: 445.1082, found: 445.1095.

1,8-Bis(benzyloxy)-5-oxooctan-4-yl methanesulfonate (9g). Prepared by general procedure 2, using **14g** (98.5 mg, 0.276 mmol, 1 eq), mesyl chloride (43 µL, 0.55 mmol, 2 eq), triethylamine (116 µL, 0.828 mmol, 3 eq), DMAP (3.5 mg. 0.028 mmol, 0.1 eq) and CH_2Cl_2 (1 mL). Dry-flash chromatography (petroleum ether/ ethyl acetate = 7/3) afforded 96.5 mg (80%) of **9g**, as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) *δ* 7.40–7.23 (m, 10H), 5.00 (dd, *J* 8.5, 4.0 Hz, 1H), 4.47 (s, 2H), 4.46 (s, 2H), 3.54–3.40 (m, 4H), 3.04 (s, 3H), 2.72–2.56 (m, 2H), 2.05–1.78 (m, 4H), 1.78–1.68 (m, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) *δ* 206.0, 138.3, 138.3, 128.5, 128.5, 127.8, 127.8,

127.7, 83.9, 73.1, 73.0, 69.1, 68.9, 38.9, 35.3, 28.5, 25.2, 23.4. **IR** (ATR) ν_{max}: 3411, 3064, 3032, 2933, 2869, 1719, 1523, 1496, 1475, 1454, 1355. **HRMS** (m/z) $[M+Na]^+$ calcd. for $C_{23}H_{30}O_6S$: 457.1655, found: 457.1658.

1,6-Bis((*N*-allyl-4-methylphenyl)sulfonamido)-4-oxohexan-3-yl methanesulfonate (9h). Prepared by general procedure 2, using **14h** (65.0 mg, 0.122 mmol, 1 eq), mesyl chloride (20 µL, 0.258 mmol, 2.12 eq), triethylamine (60 µL, 0.43 mmol, 3.54 eq), DMAP (1.5 mg. 0.012 mmol, 0.1 eq) and CH_2Cl_2 (0.2 mL) during 20 minutes. Column chromatography (toluene/ ethyl acetate = 3/1) afforded 52.1 mg (70%) of **9h**, as a yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.69 (dd, *J* 7.8, 4.8 Hz, 4H), 7.32 (dd, *J* 7.9, 2.8 Hz, 4H), 5.69–5.59 (m, 2H), 5.26–5.12 (m, 4H), 5.02 (dd, *J* 7.9, 3.8 Hz, 1H), 3.85 – 3.71 (m, 4H), 3.44–3.24 (m, 3H), 3.19 (s, 3H), 3.19–3.10 (m, 1H), 3.07 – 2.87 (m, 2H), 2.43 (s, 6H), 2.28– 2.15 (m, 1H), 2.11–1.98 (m, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 204.2, 143.7, 136.3, 136.1, 132.9, 132.5, 130.1, 130.0, 127.4 (2C), 120.2, 119.8, 52.1, 51.7, 43.3, 42.2, 39. 1, 38.9, 30.5, 21.7, 21.7. **IR** (ATR) ν_{max}: 3028.8, 2929.2, 1703.2, 1342.7, 1159.2, 1092.2, 938.2, 549.7. **HRMS** (m/z) $[M-H]^+$ calcd. for $C_{27}H_{36}N_2O_8S_3$: 635.1531, found: 635.1542.

1,6-Bis(benzylthio)-4-oxohexan-3-yl methanesulfonate (9i). Prepared by general procedure 2, using **14i** (60.5 mg, 0.168 mmol, 1 eq), mesyl chloride (26 µL, 0.335 mmol, 2 eq), triethylamine (70 µL, 0.503 mmol, 3 eq), DMAP (2.3 mg. 0.017 mmol, 0.1 eq) and CH_2Cl_2 (0.42 mL) during 20 minutes. Column chromatography (benzene/ ethyl acetate = 925/75) afforded 56.2 mg (72%) of **9i**, as a yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36–7.22 (m, 10H), 5.02 (dd, *J* 6.9, 5.4 Hz, 1H), 3.75–3.67 (m, 4H), 3.04 (s, 3H), 2.75–2.63 (m, 4H), 2.61–2.45 (m, 2H), 2.03 – 1.93 (m, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 204.5, 138.3, 138.0, 129.0 (2C), 128.8, 128.7, 127.4, 127.3, 82.1, 38.9, 38.8, 37.0, 36.3, 30.8, 26.5, 24.9. **IR** (ATR) ν_{max}: 3093, 3060, 3027, 2925, 1729, 1601, 1494, 1452, 1419. **HRMS** (m/z) $[M+Na]^+$ calcd. for $C_{21}H_{26}O_4S_3$: 461.0891, found: 461.0892.

4-Oxo-1,6-diphenylhexan-3-yl methanesulfonate (9j). Prepared by general procedure 2, using **14j** (100 mg, 0.37 mmol, 1 eq), mesyl chloride (43 µL, 0.56 mmol, 1.5 eq), triethylamine (130 µL, 0.925 mmol, 2.5 eq), DMAP (9 mg. 0.037 mmol, 0.1 eq) and CH_2Cl_2 (1.7 mL) during 20 minutes. Dry-flash chromatography (petroleum ether/ ethyl acetate = 75/25) afforded 92.5 mg (72%) of **9j**, as colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.34–7.12 (m, 10H), 4.94 (dd, *J* 7.7, 4.7 Hz, 1H), 3.07 (s, 3H), 3.02–2.87 (m, 2H), 2.87–2.78 (m, 2H), 2.74–2.66 (m, 2H), 2.14–1.97 (m, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 205.4, 140.6, 139.9, 128.9, 128.8 (2C), 128.7, 128.6, 128.5, 126.8, 126.6, 83.2, 40.5, 39.1, 33.0, 31.1, 29.3. **IR** (ATR) ν_{max}: 3085, 3061, 3028, 2858, 1730, 1603, 1521, 1496, 1453, 1411, 1359. **HRMS** (m/z) $[M+K]^+$ calcd. for $C_{19}H_{24}O_4S$: 385.0870, found: 385.0879.

General procedure 3. Preparation of cyclopropanone hemiacetals.[11] Triethylamine (1.1-1.6 eq) was added to the solution of mesylate **9** (1 eq) in 2,2,2-trifluoroethanol (0.07-0.26 M) and the reaction mixture was stirred at 0-45 °C for 0.5-27 h, under an argon atmosphere. The reaction mixture was carefully concentrated *in vacuo* and the residue was purified by column chromatography to afford cyclopropenone hemiacetals **11**.

2-(2-((3-Methylbut-2-en-1-yl)oxy)ethyl)-3-(((3-methylbut-2-en-1-yl)oxy)methyl)-1-(2,2,2-trifluoroethoxy)cyclopropan-1-ol (11a). Method I: Prepared by general procedure 3, using mesylate **14a**[Error! Bookmark not defined.] (10.8, 0.029 mmol, 1 eq), triethylamine (4.6 µL, 0.032 mmol, 1.1 Eq) and trifluoroethanol (0.135 mL) at 0 °C, during 27 h. Purification by column chromatography (petroleum ether/ethyl acetate=5/1) afforded 5.5 mg (61%) of compound **11a,** as colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.62 (s, 1H), 5.39–5.30 (m, 2H), 4.07–3.85 (m, 6H), 3.67–3.55 (m, 2H), 3.50–3.40 (m, 2H), 1.91 (d, *J* 13.8 Hz, 1H), 1.74 (d, *J* 5.5 Hz, 3H), 1.67 (d, *J* 7.2 Hz, 3H), 1.70–1.46 (m, 2H), 1.38 (td, *J* 11.0, 4.2 Hz, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 138.6, 137.1, 124.1 (q, *J* 277.3 Hz), 121.3, 120.0, 88.4, 69.6, 67.8, 67.2, 65.0, 63.6 (d, *J* 34.5 Hz), 28.2, 27.0, 25.9, 25.8, 24.2,

18.1 (2C). **IR** (ATR) ν_{max}: 3251, 2973, 2925, 2865, 1756, 1675, 1450, 1413, 1379. **HRMS** (m/z) $[M+NH_4]^+$ calcd. for $C_{18}H_{29}F_3O_4$: 384.2356, found: 384.2417.

Method II: Prepared by general procedure 3, using mesylate **14a**[Error! Bookmark not defined.] (28.1, 0.077 mmol, 1 eq), triethylamine (17 µL, 0.124 mmol, 1.6 Eq) and trifluoroethanol (0.25 mL) at 45 °C, during 3.5 h. Purification by column chromatography (petroleum ether/ethyl acetate=9/1) afforded 14.9 mg (53%) of compound **11a** (inseparable mixture with 3% of Favorskii ester **12a,** according to ^{1}H NMR) and 5.4 mg (26%) of compound **10a**, both as colorless oils.

4-((3-Methylbut-2-en-1-yl)oxy)-1-(4-(prop-1-en-2-yl)tetrahydrofuran-3-yl)butan-1-one (10a).[11] **^{1}H NMR** (400 MHz, $CDCl_3$) *δ* 5.34 – 5.28 (m, 1H), 4.85 – 4.81 (m, 2H), 4.03 (t, *J* 8.4 Hz, 1H), 3.98 (t, *J* 8.1 Hz, 1H), 3.95 – 3.89 (m, 3H), 3.65 (dd, *J* 7.2 Hz, 1H), 3.40 (t, *J* 6.4 Hz, 2H), 3.17 (dd, *J* 14.9, 7.3 Hz, 1H), 3.10 (dd, *J* 14.7, 7.4 Hz, 1H), 2.62 – 2.48 (m, 2H), 1.90 – 1.83 (m, 2H), 1.76 (s, 3H), 1.74 (s, 3H), 1.66 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) *δ* 209.2, 143.5, 136.9, 121.1, 112.5, 72.5, 70.2, 68.9, 67.2, 55.7, 50.2, 39.4, 25.8, 23.7, 20.0, 18.0.

2-(2-(((*E*)-But-2-en-1-yl)oxy)ethyl)-3-((((*E*)-but-2-en-1-yl)oxy)methyl)-1-(2,2,2-trifluoroethoxy)cyclopropan-1-ol (11b). Prepared by general procedure 3, using mesylate **9b**[11] (17.3 mg, 0.052 mmol, 1 eq), triethylamine (12 µL, 0.083 mmol, 1.6 eq) and 2,2,2-trifluoroethanol (0.2 mL) during 0.5 h. Purification by column chromatography (petroleum ether /ethyl acetate = 8 /2) afforded 8.5 mg (48%) of **11b** as a colorless oil (inseparable mixture with Favorskii ester in a relative ratio 6.7 :1 according to ^{1}H NMR). In this reaction, formation of THF-derivative in small quantities (up to 10%) was also observed. **^{1}H NMR** (500 MHz, $CDCl_3$) *δ* 5.80–5.63 (m, 2H), 5.62–5.50 (m, 3H), 4.43 (q, *J* 8.6 Hz, 2H-**Favorskii ester**), 4.07–3.80 (m, 6H), 3.66–3.54 (m, 2H), 3.50–3.36 (m, 2H), 2.80–2.72 (m, 1H-**Favorskii ester**), 2.00–1.58 (m, 10H), 1.57–1.47 (m, 1H), 1.38 (td, *J* 11.1, 4.5 Hz, 1H-**11b**). **^{13}C NMR** (126 MHz, $CDCl_3$) *δ* 174.5, 131.0, 129.6, 129.5, 127.8, 127.7, 127.5, 126.6, 125.3, 124.2 (q, *J* 277.8 Hz), 88.5, 72.2, 71.8, 71.5, 69.8, 67.6, 64.9, 63.6 (q, *J* 34.3 Hz), 39.9, 32.5, 28.1, 26.9, 24.1, 21.2, 17.9, 17.8.

2-(2-(((*Z*)-But-2-en-1-yl)oxy)ethyl)-3-((((*Z*)-pent-3-en-1-yl)oxy)methyl)-1-(2,2,2-trifluoroethoxy)cyclopropan-1-ol (11c). Prepared by general procedure 3, using mesylate **9c**[11] (30.5 mg, 0.09 mmol, 1 eq), triethylamine (14 µL, 0.099 mmol, 1.1 eq) and 2,2,2-trifluoroethanol (0.79 mL) during 3.5 h. Purification by column chromatography (petroleum ether/ethyl acetate = 85/15) afforded 26.5 mg (87%) of a compound **11c,** as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) *δ* 5.77–5.48 (m, 5H), 4.13–3.86 (m, 6H), 3.69–3.55 (m, 2H), 3.52–3.43 (m, 2H), 1.96–1.86 (m, 1H), 1.75–157 (m, 7H), 1.57–1.47 (m, 1H), 1.40 (td, *J* 11.0, 4.3 Hz, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) *δ* 129.5, 128.0, 127.1, 125.6, 124.13 (q, *J* 277.5 Hz), 88.4, 70.0, 66.6, 66.0, 65.1, 63.6 (q, *J* 34.4 Hz), 28.1, 27.0, 24.2, 13.3, 13.2. **IR:** 3366, 3025, 2924, 2865, 1452, 1279, 1163, 1090, 967. **HRMS** (ESI) calcd. for $C_{16}H_{23}F_3O_4$ $[M+K]^+$: 377.1342, found: 377.1341**.**

2-(2-(Allyloxy)ethyl)-3-((allyloxy)methyl)-1-(2,2,2-trifluoroethoxy)cyclopropan-1-ol (11d). Prepared by general procedure 3, using mesylate **9d** (35.5 mg, 0.116 mmol, 1 eq), triethylamine (18 µL, 0.127 mmol, 1.1 eq) and 2,2,2-trifluoroethanol (0.53 mL) during 8 h. Purification by column chromatography (petroleum ether/ethyl acetate = 4/1) afforded 29.7 mg (83%) of a compound **11d,** as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) *δ* 5.91–5.85 (m, 2H), 5.39 (s, 1H), 5.34–5.14 (m, 4H), 4.10–3.97 (m, 4H), 3.97–3.86 (m, 2H), 3.67–3.61 (m, 1H), 3.61–3.55 (m, 1H), 3.53–3.43 (m, 2H), 1.95–1.85 (m, 1H), 1.67–1.49 (m, 3H), 1.41 (td, *J* 11.0, 4.4 Hz, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) *δ* 135.0, 133.8, 124.12 (q, *J* 277.6 Hz), 118.4, 117.1, 88.5, 72.6, 71.7, 70.1, 65.2, 63.7 (q, *J* 34.5 Hz), 28.0, 26.9, 24.1. **IR:** 3364, 3083, 3015, 2920, 2864, 1756, 1647, 1454, 1424, 1350, 1279.

2-(2-(But-2-yn-1-yloxy)ethyl)-3-((pent-3-yn-1-yloxy)methyl)-1-(2,2,2-trifluoroethoxy)cyclopropan-1-ol (11e). Prepared by general procedure 3, using mesylate **9e** (34.6 mg, 0.1 mmol, 1 eq), triethylamine (15 µL, 0.1

mmol, 1 eq) and 2,2,2-trifluoroethanol (1.5 mL) at room temperature during 3.5 h. Purification by column chromatography (petroleum ether/ethyl acetate = 85/15) afforded 26 mg (77%) of a mixture of compounds **11e,** as a colorless oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.13 (s, 1H), 4.22–3.96 (m, 6H), 3.70–3.61 (m, 2H), 3.59–3.52 (m, 2H), 1.96–1.89 (m, 1H), 1.87–1.81 (m, 6H), 1.69–1.62 (m, 1H), 1.62–1.52 (m, 1H), 1.40 (td, *J* 11.0, 4.4 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 124.1 (q, *J* 277.6 Hz), 88.5, 83.5, 82.5, 77.4, 77.2, 76.9, 75.3, 74.3, 69.7, 64.9, 63.7 (q, *J* 34.5 Hz), 59.2, 58.5, 27.8, 26.9, 24.0, 3.7, 3.5. **IR** (ATR) ν_{max}: 3369, 2927, 2867, 2244, 1754, 1447, 1414, 1358. **HRMS** (ESI) calcd. for $C_{16}H_{21}F_3O_4$ $[M+NH_4]^+$: 352.1730, found: 352.1744**.**

2-(2-(Benzyloxy)ethyl)-3-((benzyloxy)methyl)-1-(2,2,2-trifluoroethoxy)cyclopropan-1-ol and 2,2,2-trifluoroethyl 4-(benzyloxy)-2-(2-(benzyloxy)ethyl)butanoate (11f). Prepared by general procedure 3, using mesylate **9f** (44.7 mg, 0.11 mmol, 1 eq), triethylamine (15 µL, 0.11 mmol, 1 eq) and 2,2,2-trifluoroethanol (0.5 mL) at room temperature during 24 h. Purification by dry-flash chromatography (petroleum ether /ethyl acetate = 85 /15) afforded 40 mg (87%) of compound **11f**, as a colorless oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.40–7.26 (m, 10H), 5.30 (s, 1H), 4.61–4.53 (m, 3H), 4.49–4.45 (m, 1H), 4.07–3.97 (m, 1H), 3.90–3.78 (m, 1H), 3.73–3.67 (m, 1H), 3.66–3.60 (m, 1H), 3.57–3.50 (m, 2H), 1.97–1.87 (m, 1H), 1.70–1.50 (m, 2H), 1.44 (td, *J* 11.0, 4.1 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 138.6, 137.2, 128.8, 128.5, 128.3, 128.2, 127.8, 127.7, 124.14 (q, *J* 277.0 Hz), 88.4, 73.9, 72.9, 70.2, 65.4, 63.6 (d, *J* 34.3 Hz), 27.9, 27.0, 24.2. **IR** (ATR) ν_{max}: 3374,3089, 3065, 3031, 2927, 2865, 1755, 1496, 1454, 1411, 1365, 1277. **HRMS** (ESI) calcd. for $C_{22}H_{25}F_3O_4$ $[M+Na]^+$: 433.1597, found: 433.1611**.**

2-(2-(Benzyloxy)ethyl)-3-(3-(benzyloxy)propyl)-1-(2,2,2-trifluoroethoxy)cyclopropan-1-ol (11g). Prepared by general procedure 3, using mesylate **9g** (50.4 mg, 0.116 mmol, 1 eq), triethylamine (16 µL, 0.116 mmol, 1 eq) and 2,2,2-trifluoroethanol (0.47 mL) at room temperature during 6 h. Purification by column chromatography (toluene/ethyl acetate = 9/1) afforded 36.7 mg (72%) of a compound **11g**, as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37–7.27 (m, 10H), 5.33 (s, 1H), 4.59–4.44 (m, 4H), 3.9– 3.87 (m, 1H), 3.87–3.76 (m, 1H), 3.69–3.63 (m, 1H), 3.58–3.42 (m, 3H), 1.82–1.35 (m, 6H), 1.30–1.19 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 138.4, 137.5, 128.7, 128.5, 128.2, 127.9, 127.8, 88.6, 73.8, 73.0, 70.3, 69.9, 63.5 (d, *J* 34.2 Hz), 29.5, 28.0, 25.9, 23.8, 19.6. **IR** (ATR) ν_{max}: 3377, 3064, 3032, 2938, 2866, 1755, 1720, 1494, 1453, 1411, 1363. **HRMS** (ESI) calcd. for $C_{24}H_{29}F_3O_4$ $[M+K]^+$: 477.1655, found: 477.1659**.**

***N*-Allyl-*N*-((3-(2-((*N*-allyl-4-methylphenyl)sulfonamido)ethyl)-2-hydroxy-2-(2,2,2-trifluoroethoxy)cyclopropyl)methyl)-4-methylbenzenesulfonamide (11h).** Prepared by general procedure 3, using mesylate **9h** (52.0 mg, 0.097 mmol, 1 eq), triethylamine (14 µL, 0.097 mmol, 1 eq) and 2,2,2-trifluoroethanol (0.39 mL) at room temperature during 1.5 h. Purification by column chromatography (toluene/ethyl acetate = 85/15) afforded 42.1 mg (80%) of a compound **11h**, as a yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.74–7.58 (m, 4H), 7.35–7.27 (m, 4H), 5.74–5.53 (m, 2H), 5.27–5.07 (m, 5H), 4.03 (q, *J* 8.8 Hz, 2H), 3.88 (td, *J* 16.2, 6.4 Hz, 1H), 3.76 (td, *J* 14.3, 6.5 Hz, 3H), 3.26–3.04 (m, 4H), 2.43 (s, 3H), 2.42 (s, 3H), 1.67–1.57 (m, 2H), 1.50 (td, *J* 10.4, 3.3 Hz, 1H), 1.28–1.23 (m, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 144.0, 143.6, 136.6, 136.4, 133.1, 132.9, 130.0, 129.9, 128.7, 127.3, 124.0 (q, *J* 277.7 Hz), 119.8, 119.4, 88.3, 64.0 (d, *J* 34.6 Hz), 51.8, 51.3, 47.3, 43.2, 26.4, 24.9, 22.6, 21.7, 21.6. **IR** (ATR) ν_{max}: 3424, 2926, 1453, 1333, 1283, 1159, 1115. **HRMS** (ESI) calcd. for $C_{28}H_{35}F_3N_2O_6S_2$ $[M+Na]^+$: 639.17863, found: 639.17973**.**

2-(2-(Benzylthio)ethyl)-3-((benzylthio)methyl)-1-(2,2,2-trifluoroethoxy)cyclopropan-1-ol (11i). Prepared by general procedure 3, using mesylate **9i** (100.4 mg, 0.228 mmol, 1 eq), triethylamine (31.5 µL, 0.228 mmol, 1 eq) and 2,2,2-trifluoroethanol (1.7 mL) at 0 °C during 5 h. Purification by column chromatography (petroleum ether/ethyl acetate = 99/1) afforded 42.8 mg of desired compound (ca. 80% purity), that was further purified

to afford 8 mg (8%) of compound **11i**, as colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40–7.18 (m, 10H), 4.10–3.90 (m, 2H), 3.80–3.60 (m, 4H), 2.75–2.19 (m, 2H), 1.92–1.18 (m, 1H).

2-Benzyl-3-phenethyl-1-(2,2,2-trifluoroethoxy)cyclopropan-1-ol (11j). Prepared by general procedure 3, using mesylate **9j** (59.3 mg, 0.17 mmol, 1 eq), triethylamine (24 µL, 0.17 mmol, 1 eq) and 2,2,2-trifluoroethanol (0.7 mL) during 2 h. Purification by dry-flash chromatography (benzene/ethyl acetate = 98/2) afforded 38 mg (64%) of a compound **11j,** as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37–7.10 (m, 10H), 3.82–3.69 (m, 1H), 3.69–3.56 (m, 1H), 2.85–2.75 (m, 1H), 2.67–2.57 (m, 3H), 1.96–1.84 (m, 1H), 1.72–1.60 (m, 1H), 1.52–1.45 (m, 1H), 1.38–1.30 (m, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 141.6, 141.1, 128.7, 128.6, 128.5, 128.5, 128.4, 128.2, 126.2, 126.0, 89.2, 63.6 (d, *J* 34.4 Hz), 35.7, 28.8, 28.4, 27.7, 25.0. **IR** (ATR) ν_{max}: 3509, 3086, 3063, 3028, 2929, 2860, 1754, 1720, 1603, 1496, 1454, 1415. **HRMS** (ESI) calcd. for $C_{20}H_{21}F_3O_2$ $[M+K]^+$: 389.1131, found: 389.1115**.**

Cyclization reaction of oxyallyl cation derived from 2,2.2-trifluoroethoxy hemiacetal (11a). Triethylamine (1.9 µL, 0.013 mmol, 1.1 eq) was added to a solution of **11a** (4.4 mg, 0.012 mmol, 1 eq) in trifluoroetanol (0.1 mL) and the reaction mixture was stirred at room temperature for 4 h. The reaction mixture was carefully concentrated *in vacuo* and the residue was purified by column chromatography (petroleum ether/ethyl acetate = 6/1) to afford 1.8 mg of compound **12a** (41%) and 1.5 mg (47%) of compound **10a**, as colorless oils.

2,2,2-Trifluoroethyl 4-((3-methylbut-2-en-1-yl)oxy)-2-(2-((3-methylbut-2-en-1-yl)oxy)ethyl)butanoate (12a). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.30 (td, *J* 6.9 Hz, 2H), 4.44 (q, *J* 8.5 Hz, 2H), 3.90 (d, *J* 6.9 Hz, 4H), 3.47–3.35 (m 4H), 2.82–2.73 (m, 1H), 2.03–1.90 (m, 2H), 1.84–1.75 (m, 2H), 1.73 (s, 6H), 1.65 (s, 6H).

(4+3) Cycloaddition reaction of oxyallyl cation derived from 2,2.2-trifluoroethoxy hemiacetal (11f). To a solution of **11f** (49.6 mg, 0.12 mmol, 1 eq) and furan (72 µL, 0.98 mmol, 8 eq) in trifluoroetanol (0.7 mL) was added triethylamine (18 µL, 0.13 mmol, 1.1 eq) and the reaction mixture was stirred at 45 °C during 12 h. The reaction mixture was carefully concentrated *in vacuo* and the residue was purified by column chromatography (petroleum ether/ethyl acetate = 75/25) to afford 17.4 mg (38%) compound *endo*-**15**, 5.8 mg (13%) of compound *exo*-**15** and 14 mg (29%) of compound **12f**, as colorless oils.

2,4-*endo*,*cis*-2-(2-(Benzyloxy)ethyl)-4-((benzyloxy)methyl)-8-oxabicyclo[3.2.1]oct-6-en-3-one (*endo*-15). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.34–7.20 (m, 10H), 6.23 (d, *J* 6.2 Hz, 1H), 6.17 (d, *J* 6.1 Hz, 1H), 5.12 (d, *J* 4.4 Hz, 1H), 4.97 (d, *J* 4.5 Hz, 1H), 4.55–4.38 (m, 4H), 3.81 (dd, *J* 10.1, 4.7 Hz, 1H), 3.61–3.53 (m, 1H), 3.52–3.44 (m, 1H), 3.27 (t, *J* 9.8 Hz, 1H), 3.08 (dt, *J* 9.0, 4.6 Hz, 1H), 2.83 (q, *J* 5.8 Hz, 1H), 2.09–1.99 (m, 1H), 1.33–1.29 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 208.0, 139.2, 1347, 134.4, 129.6, 128.9, 128.8 (2C), 82.6, 81.1, 74.5, 74.2, 69.6, 67.3, 56.7, 54.2, 26.7.

2,4-*exo*,*cis*-2-(2-(Benzyloxy)ethyl)-4-((benzyloxy)methyl)-8-oxabicyclo[3.2.1]oct-6-en-3-one (*endo*-15). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.40–7.25 (m, 10H), 6.30–6.19 (m, 2H), 5.01 (s, 1H), 4.78 (s, 1H), 4.58–4.40 (m, 4H), 3.81 (dd, *J* 9.5, 1H), 3.60 (dd, *J* 8.8, 5.5 Hz, 1H), 3.57–3.47 (m, 2H), 2.60 (dd, *J* 10.0, 5.3 Hz, 1H), 2.39 (t, *J* 7.5 Hz, 1H), 2.04–1.84 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 209.0, 138.4, 138.0, 133.8 (2C), 128.6, 128.5, 127.9, 127.8, 80.4, 78.1, 73.3, 73.0, 69.7, 67.7, 56.6, 52.4, 31.2.

2,2,2-Trifluoroethyl 4-(benzyloxy)-2-(2-(benzyloxy)ethyl)butanoate (12f). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37–7.23 (m, 10H), 4.52–4.39 (m, 4H), 4.25 (q, *J* 8.5 Hz, 2H), 3.54–3.42 (m, 4H), 2.89–2.79 (m, 1H), 2.06–1.94 (m, 2H), 1.89–1.76 (m, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 174.5, 138.3, 128.5, 127.8 (2C), 123.2 (q, *J* 277.3 Hz), 73.2, 67.9, 60.2 (q, *J* 36.4 Hz), 39.9, 32.4.

Computational details All DFT calculations were performed with the ADF[27] engine in the Amsterdam Modeling Suite (version 2023.104)[28]. The all-electron triple-zeta Slater-type orbitals plus one polarization function (TZP) basis set was used for all atoms. Geometry optimizations were done with the B97-D[29] exchange-correlation functional from the LibXC library.[30] The COSMO solvation model, as implemented in ADF,[31] was used, with trifluoroethanol as the solvent (the dielectric constant 26.726; the radius of solvent molecules 3.05 Å). The harmonic frequencies were calculated at the same level of theory. The vibrational analysis in the quasi-harmonic approximation, as proposed by Truhlar[32,33] (frequency cut-off 100 cm^{-1}), was used to evaluate the zero-point effects and the entropic and thermal corrections to the Gibbs free energy at 298.15K. Since the vibrational analysis is carried out in the standard state of 1 atm, a conversion to the standard state of 1 mol dm^{-3} solution is done (correction of the free energies for 1.89 kcal mol^{-1} at 298.15K). For reactions involving trifluoroethanol, the free energy correction due to the conversion to the solvent standard state is made (3.45 kcal mol^{-1}, at 298.15K). The electronic energies used to calculate the Gibbs free energy were evaluated using the double-hybrid rev-DOD-PBEP86-D4 functional.[16]

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Supplementary Material

Copies of NMR spectra for synthesized compounds are available as a separate document (Title: SM_Cyclopropanone Hemiacetals.

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