



Studies on fluorofunctionalization of some functionalized alkene scaffolds

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ABSTRACT

A study on some halo-fluorination and fluoroselenation protocols of various functionalized cyclic olefins, such as esters, lactams or amino esters as model compounds is presented. The ring olefin bond functionalizations were based on their activation either with NBS, NIS or PhSeBr followed by treatment with nucleophilic fluorinating agents, such as Deoxo-Fluor. The attempted synthetic assays have been found to be highly substrate dependent, influenced by the nature of the functional groups present on the cycloalkene skeleton as well as the stereostructural architecture of the starting model compounds.

Introduction

Thanks to the unique properties of the fluorine atom and the C–F bond [1,2], organofluorine compounds are of high importance in medicinal chemistry and drug research [3,4]. Therefore, the construction of fluorine-containing scaffolds is a rapidly developing area of organic syntheses. The reason is that, due to the high electronegativity of the fluorine atom (EN = 3.98) and the strength of the carbon–fluorine bond, by replacing the C–H unit with a C–F unit in an organic compound, the physicochemical and biological properties of the molecule can be changed [5]. The beneficial effects achieved thereby are as follows: the polarity (lipophilicity/hydrophilicity balance) and the acid-base properties of the molecule can be influenced; moreover, the metabolic stability of fluoro-pharmaceuticals is often increased (for example, *cabotegravir* antiretroviral drug) (Fig. 1) [6]. Altogether, improved bioactivity, bioavailability, and increased affinity can be reached (for example, *sitagliptin* antidiabetic drug) (Fig. 1), without drastically changing the parent structure of the potential drug molecule, as fluorine is the second-smallest atom after hydrogen (van der Waals radii are 1.47 Å for fluorine and 1.20 Å for hydrogen) [7]. Consequently, it is not surprising that 25–30 % of small-molecule drugs in clinical use are now organofluorine compounds [3–6,8,9].

While the fluorination of organic derivatives is an all-time relevant

issue of synthetic chemistry, there is a permanent need for the development of methodologies enabling the construction of new fluorinated chemical entities. Fluorofunctionalization can be accomplished by several ways, including direct fluorination [10–12] or the incorporation of synthetically versatile fluorinated building blocks [13,14] and functional groups, for example, trifluoromethylations [15–19]. Principally, depending on the type of the fluorinating agent, three possible approaches – electrophilic, radical or anionic – exist to introduce fluorine-containing substituents into organic substrates [20]. For mono-fluorination, either electrophilic or nucleophilic reagents can be utilized [21,22]. Earlier, electrophilic fluorination methods were mainly realized with the employment of CsSO₄F, HOF, CF₃OF, XeF₂ or F₂ [23,24]. Nowadays, however, their use is limited. At present, the most frequently applied F-derived electrophilic N–F reagents are Selectfluor, N-fluorobenzenesulfonimide (NFSI), and N-fluoropyridinium salts [25–27]. Compared to electrophilic fluorinating reagents, numerous nucleophilic counterparts are known. In addition to the classical nucleophilic replacement reagents such as tetrabutyl ammonium fluoride (TBAF), silver fluoride (AgF) or potassium hydrogen difluoride (KHF₂), there are also a few examples, where sulfonates are used with a buffered HF source of fluoride such as perfluoro-1-butanefluoronyl fluoride (PBSF) [28]. Additionally, anhydrous HF and the derived amine/HF reagents, such as triethylamine tris(hydrogenfluoride) (Et₃N·3HF) and pyridinium

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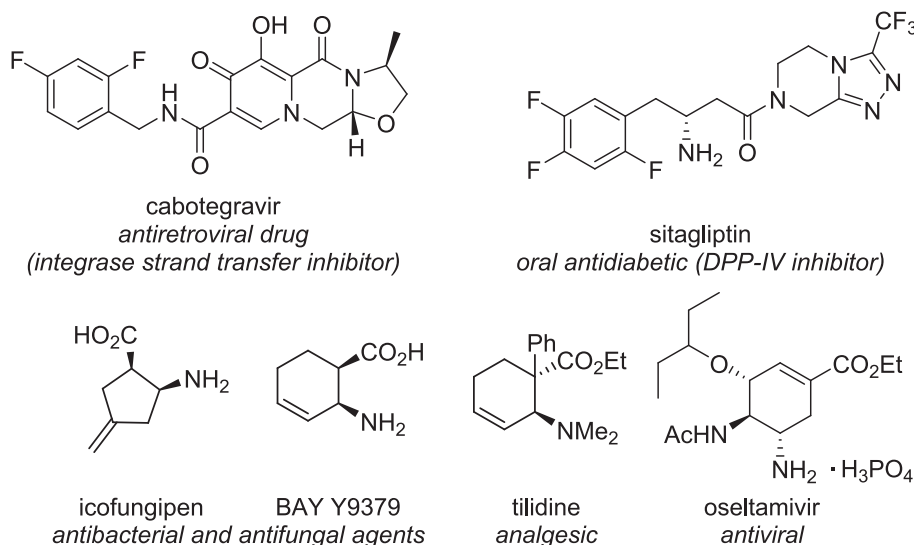


Fig. 1. The structure of some fluorine-containing drugs and bioactive cyclic β -amino acid derivatives.

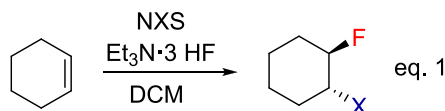
poly(hydrogenfluoride) (Pyr·9HF, Olah's reagent) may also be used. The latter is employed as a mild fluoride source. Furthermore, SF₄ and its derivatives such as diethylaminosulfur trifluoride (DAST) [29], bis(2-methoxyethyl)aminosulfur trifluoride (Deoxo-Fluor) [30], or the hindered arylsulfur trifluoride (Fluolead) [31] and crystalline amino-difluorosulfonium tetrafluoroborate salts (XtalFluor-E and XtalFluor-M) [32] are also known and utilized mostly for deoxyfluorination reactions.

Within fluoro-functionalizations, halofluorinations belong to the most efficient approaches for the introduction of fluorine into organic molecules. The easiest way of obtaining halofluorides is the halofluorination

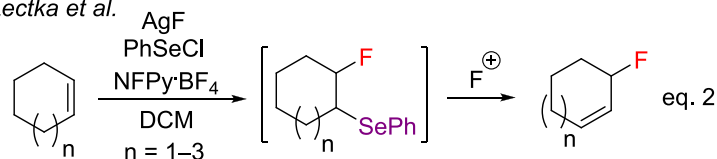
reaction of alkenes. In this case, fluorine and another halogen (chlorine, bromine or iodine) are attached to the alkene double bond. Concerning the mechanism of these transformations, two reaction types can be distinguished. In the first type, called direct halofluorination, the reagent, such as BrF or IF, provides both the electrophilic halonium ion and the nucleophilic fluoride anion. In the second type, called indirect halofluorination (or "late-stage" fluorination), two individual reagents provide the halonium ion and the fluoride anion, respectively. In most of the cases, the combination of halonium ion sources, such as *N*-halogensuccinimides (NXS) [33] or other *N*-halogen compounds (for

Previous work

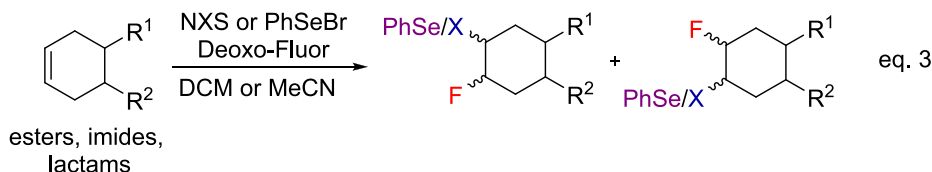
Marciniak et al.



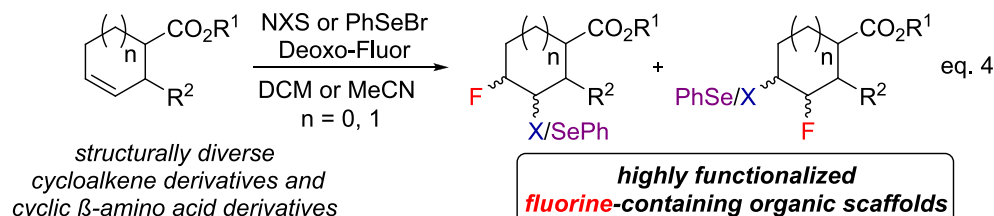
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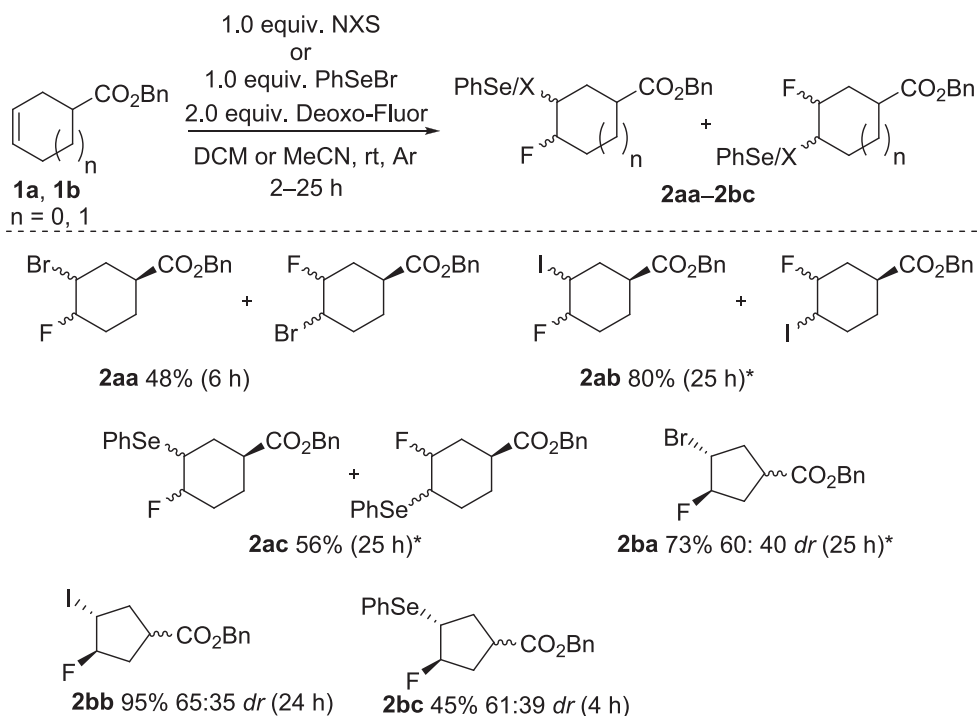
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This work



Scheme 1. Halo- and selenofluorination strategies for the construction of fluorinated scaffolds.



Scheme 2. Halo- and selenofluorinations of cyclohexene and cyclopentene benzyl esters.

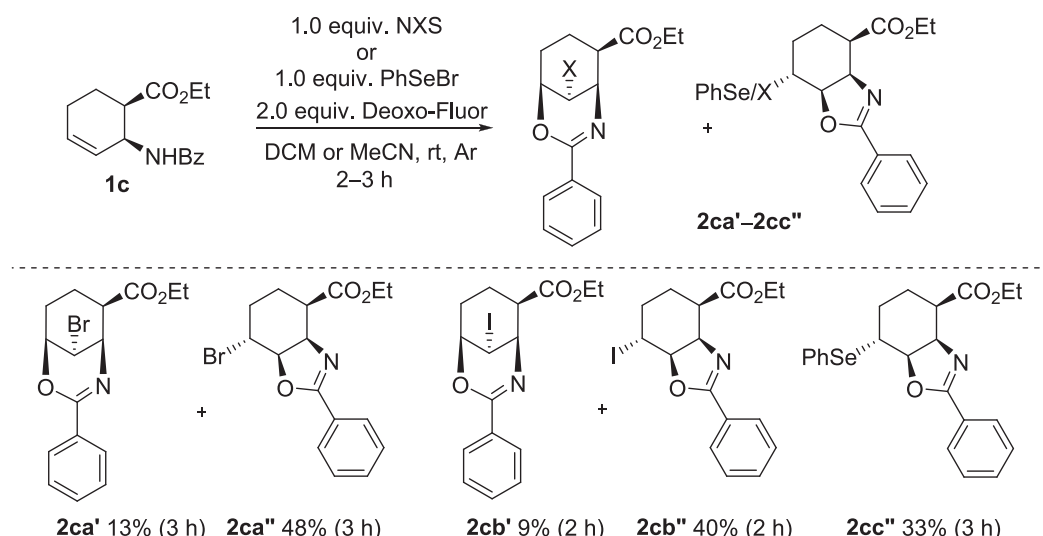
example, 1,3-dibromo-5,5-dimethylhydantoin, DBH [34] and a fluoride reagent, specifically $\text{Et}_3\text{N}\cdot 3\text{HF}$, $\text{Pyr}\cdot 9\text{HF}$ or different kinds of HF salts [35] are applied. Beyond halofluorinations, selenofluorination of alkenes is another promising approach for fluorine incorporation. One possibility to get the target addition products of “PhSeF” across the double bond is the application of benzeneselenenyl bromide or chloride (PhSeX) in combination with silver(I) fluoride [36,37], while the employment of *N*-(phenylseleno)phthalimide (NPSePh) with $\text{Et}_3\text{N}\cdot 3\text{HF}$ or $\text{Pyr}\cdot 9\text{HF}$ was also described [38,39]. Furthermore, applying diphenyldiselenide (PhSeSePh) with difluoroiodotoluene (DFIT) also provided the desired fluoroselenylated products [40].

β -Amino acids – especially cyclic representatives – and their derivatives have particular importance concerning their aspects in

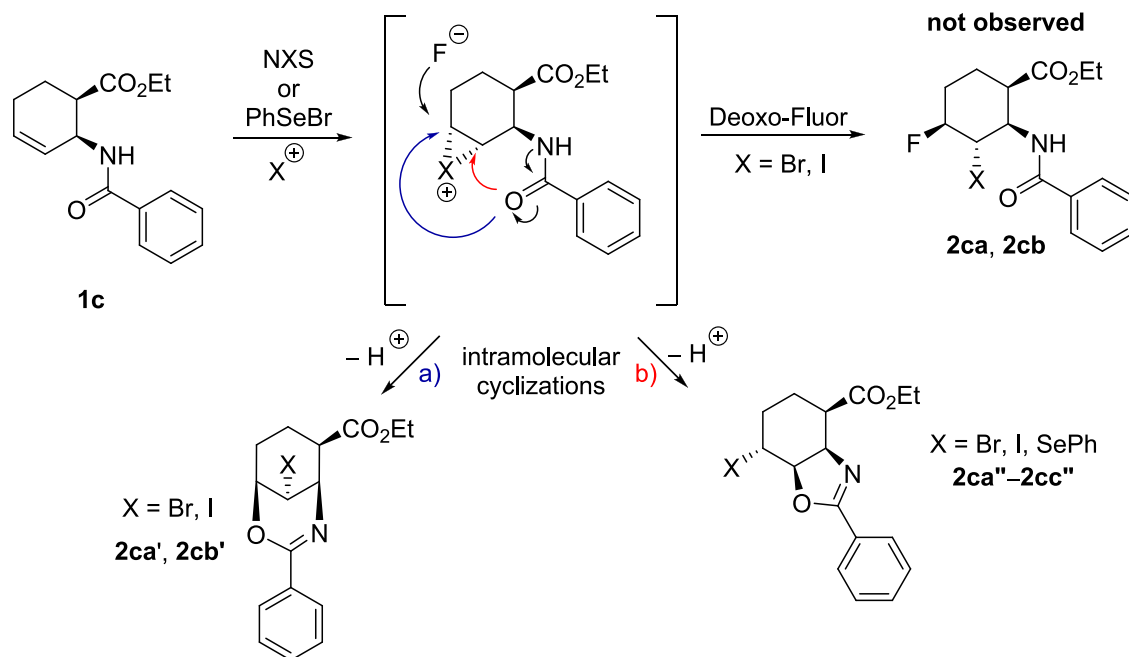
medicinal and peptide chemistry or in chemical biology [41]. Several natural or synthetic cyclic amino acid derivatives, some of them are approved drug molecules or their chiral building block, show relevant biological activity. Representative examples are *icofungipen* antibacterial and antifungal agent, *tilidine* analgesic or *oseltamivir* antiviral drugs (Fig. 1) [42,43]. Thus, the synthetic need for analogues of functionalized cyclic amino acid derivatives and bioactive compounds is unquestionable. As a result, their synthesis has increasingly become the focus of organic transformations in the last two decades [44–49].

Aims

On the basis on protocols reported earlier by Marciniak (Scheme 1,



Scheme 3. Functionalization of *N*-benzoyl cyclohexene amino ethyl ester **1c** (for similar compounds see also ref. 47–49).



Scheme 4. Proposed pathways of the functionalization of substrate **1c**.

Eq. (1) [33]a and Lectka (Scheme 1, Eq. (2) [37], Haufe [33]b and Olah^{33c} we have explored the applicability of the possible nucleophilic fluorinating agents. A novel approach for the synthesis of new fluorinated building blocks *via* the halo- and selenofluorination of cyclic olefins such as diesters, imides, and lactams applying NXS/Deoxo-Fluor and PhSeBr/Deoxo-Fluor systems was described by our research group (Scheme 1, eq. 3) [50].

We aimed to extend the use of our halo- and selenofluorination concept to novel starting model compounds, such as structurally diverse cycloalkene and cyclic β -amino acid derivatives, possessing relevant pharmaceutical attributions (Scheme 1, eq. 4). Beyond the importance of the conceptual aspects of the transformation, the realization of the designed chemical approach should provide a new synthetic route to highly functionalized fluorine-containing organic scaffolds with promising biological effects.

Results and discussion

To realize the concept, first monosubstituted five- and six-membered cycloalkene benzyl esters were selected as substrates and examined in halo- and selenofluorination reactions. The treatment of benzyl (*S**)-cyclohex-3-ene-1-carboxylate (**1a**) with NBS or NIS and Deoxo-Fluor, performed at room temperature in DCM, provided the corresponding bromo- and iodo-fluorinated products (**2aa** and **2ab**) as mixture of regioisomers in 48 % and 80 % yields (Scheme 2). Then, the reaction of **1a** in the presence of Deoxo-Fluor and PhSeBr in MeCN led to the appropriate selenofluorinated product (**2ac**) in 56 % yield. When halo-fluorination with the corresponding cyclopentene benzyl ester (**1b**) was attempted, the desired products (**2ba** and **2bb**) were isolated as diastereomers in good and excellent yields (73 % and 95 %). The corresponding five-membered selenofluorinated analogue (**2bc**) was obtained as diastereoisomers in a yield of 45 %.

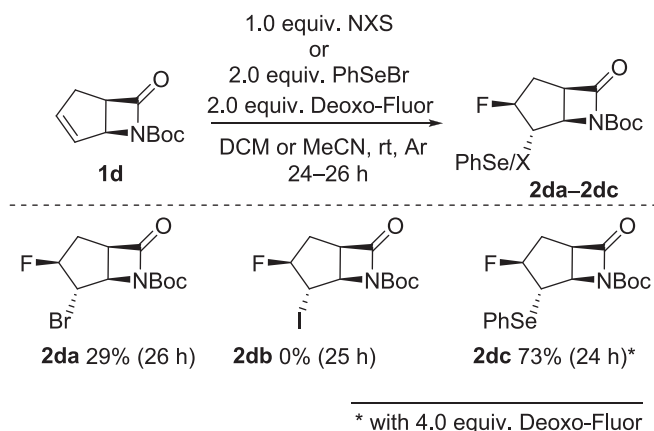
Since the fluorination of both cycloalkene starting model compounds yielded an inseparable mixture of regio- or stereoisomers of halo-fluorinated scaffolds, we have focused on difunctionalized cyclic amino esters with a cycloalkene core owing to their higher structural diversity. We assumed that employing starting materials with higher anchimeric and functional group directing effects, the regioselective reaction would result separable products. Therefore, *N*-benzoyl

cyclohexene amino ethyl ester (**1c**) was reacted with NBS or NIS and Deoxo-Fluor. However, instead of the formation of the desired halo-fluorinated products (**2ca** and **2cb**), six- and five-membered ring-fused derivatives were obtained (Scheme 3). This can be explained by the different nucleophilicity of the oxygen and fluorine atoms (hard and soft nucleophiles, respectively, according to Pearson's HSAB theory). The corresponding oxazine products (**2ca'** and **2cb'**) were isolated in yields of 13 % and 9 %, while oxazoline derivatives **2ca''** and **2cb''** were provided in 48 % and 40 % yields, respectively. Note that similar transformations across olefin bond functionalization of cyclohexene or cyclopentene β -amino esters with halogen by participation of the internal nucleophilic amide or carbamate O atom were earlier observed in our group (46–49). Examining the reactivity of substrate **1c** toward selenofluorination reaction, applying Deoxo-Fluor and PhSeBr in MeCN gave only the phenylselenenylated cyclized oxazoline derivative (**2cc''**) in 33 % isolated yield, while the desired phenylselenofluorinated product (**2cc'**) was not afforded in the transformation.

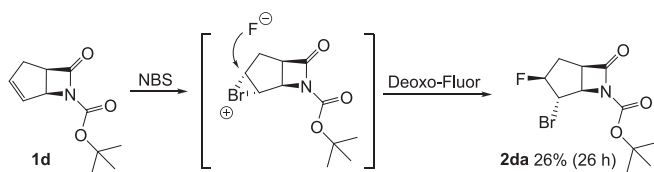
Similar findings regarding the anchimeric assistance of the neighboring groups have been described by Fustero and co-workers [51].

Next, the comprehensive investigation of the reaction parameters of bromofluorination of **1c** was implemented. The reaction was repeated using other solvents (DCE, THF, Et₂O, toluene, MeCN, and 1,4-dioxane) at room temperature and elevated temperature (50 °C and 100 °C). However, according to LC-MS analysis, either the presence of the unreacted starting material or the full consumption of **1c** with the formation of the undesired cyclized products was observed. The reaction was also attempted in the presence of XtalFluor-M as the fluorine source. Again, the formation of the ring-closed derivatives was preferential over the desired bromofluorinated compound. On the basis on our protocol developed previously [50], we attempted to enhance the decomposition of the fluorinating reagent and, therefore, to make the fluorination reaction faster. The addition of one drop of EtOH was tried at different temperatures (room temperature, 40 °C and 100 °C) and in the excess of the fluorine source (2.0 equiv), but no bromofluorinated product was detected. The same result was achieved employing 10 mol% PTAB instead of NBS. No reaction occurred by adding three drops of EtOH at 100 °C in dioxane with the excess of fluorinating agent (5.0 equiv Deoxo-Fluor and 2.5 equiv XtalFluor-M) in the absence of NBS.

In continuation, we investigated the reaction parameters of the



Scheme 5. Halo- and selenofluorinations of *N*-Boc protected *cis*-β-lactam **1d**.



Scheme 6. Plausible mechanism of the bromofluorination reaction of substrate **1d**.

selenofluorination of substrate **1c**. Utilizing other solvents such as DCM, DCE, THF, 1,4-dioxane, and toluene at room temperature or at higher temperature (50 °C and 100 °C), we were not able to detect the formation of the phenylselenenylfluorinated product, only the undesired oxazoline-derived product was produced. Neither the use of PhSeBr in excess (2.0 and 3.0 equiv) nor the replacement of Deoxo-Fluor with XtalFluor-M resulted in the formation of the desired product.

Regarding the possible pathway of the halo- and selenofluorination of substrate **1c**, we propose that in the first step of the reaction the halonium ion is attached to the double bond with a stereochemistry opposite to that of the benzoyl group (Scheme 4). Next, the reaction proceeds via three possible pathways. The attack of the fluoride anion from behind the plane of the cyclohexane ring leading to the desired halofluorinated products (**2ca** and **2cb**) did not take place. Instead, intramolecular cyclizations followed by deprotonation affording the five- and six-membered cyclized oxazine (**2ca'** and **2cb'**) and oxazoline derivatives (**2ca''–2cc''**) occur.

Expanding the substrate scope of our developed protocol, we finally examined the reactivity of *N*-Boc protected *cis*-β-lactam **1d** in halo- and selenofluorination reactions. Due to steric and functional group directing effects, we expected that substrate **1d** leads to the expected products via a regio- and stereoselective manner. Thus, when *tert*-butyl (1*R**,5*S**)-7-oxo-6-azabicyclo[3.2.0]hept-3-ene-6-carboxylate (**1d**) was reacted with NBS and Deoxo-Fluor, we were pleased to observe that the appropriate bromofluorinated derivative (**2da**) was obtained regioselectively, (with the fluoride located furthest from the lactam *N*-atom) as a single product in 29 % yield without any regio- or stereoselectivity issues (Scheme 5), whose structure was certified by means of 2D NMR analysis. In contrast, the iodofluorination of substrate **1d**, implemented in the presence of NIS and Deoxo-Fluor, was unsuccessful to give compound **2db**. Specifically, no conversion of the starting material was observed. When the selenofluorination reaction was attempted, the excess of NBS and PhSeBr was needed, and the corresponding selenofluorinated product (**2dc**) was afforded in a 73 % isolated yield.

Concerning the mechanism of the bromofluorination reaction of lactam **1d**, in accordance with our previous experiments with the *N*-Boc protected Vince-lactam (**50**), the bromonium ion is attached to the

opposite side of the lactam ring in the first step of the transformation. Next fluorine is built to the position further away from the *N* atom of the lactam functional group, with opposite stereochemistry relative to the bromine resulting in product **2da** (Scheme 6).

Conclusions and outlook

Our study on the investigation of halo- and selenofluorination of some functionalized cycloalkenes provides an insight into the attempt for incorporation of a fluorine atom into the skeleton of such unsaturated scaffolds. In the case of simple monosubstituted cycloalkenes, most of our fluorination experiments gave mixtures of fluorine-containing scaffolds. However, by increasing the variation on the structural architecture of the starting compounds (cyclic β-amino acid and β-lactam), successful functionalizations could be conducted. Namely, it was found that fluorofunctionalizations, based on halo- and selenofluorination described earlier, were highly reagent and substrate dependent. To summarize, our intention of this paper was to provide a preliminary insight into the attempts on the functionalization of some cycloalkene derivatives, with structural and functional diversity, performed across halo- and selenofluorination of unsaturated compounds. All performed fluorination protocols have been found to be highly substrate dependent and these processes are directed by functional groups. Therefore, further extensions involving novel model compounds as well as experimental conditions (reagents, solvents, additives, etc.) and studies on this simple but interesting methodology are currently continued in our laboratory.

Experimental section

General methods

Halo- and selenofluorination reactions of substrates **1a–1f** with appropriate reagents (NBS, NIS, PhSeBr, Deoxo-Fluor, XtalFluor-M) were performed under an argon atmosphere. For the reactions, dry DCM and MeCN suitable for HPLC were utilized. Unless otherwise noted, all commercial reagents were used without further purification. ¹H NMR and ¹³C NMR spectra were recorded at 300 and 75 MHz using CDCl₃ as solvent. Chemical shifts are given in ppm relative to TMS for CDCl₃. Coupling constants (*J*) are reported in hertz (Hz). HRMS data for new compounds were obtained using a Q-TQF high-resolution mass spectrometer equipped with an electrospray ion source. The measured melting points are uncorrected.

General procedure A for halofluorination reactions

Benzyl (*S**)-cyclohex-3-ene-1-carboxylate (216 mg, 1.00 mmol) and *N*-bromosuccinimide (0.178 g, 1.00 mmol) or *N*-iodosuccinimide (0.225 g, 1.00 mmol) were added to a 25 mL round-bottom flask fitted with a rubber septum, then the system was charged with argon. Dry dichloromethane (10 mL) was added under argon atmosphere, then Deoxo-Fluor (50 % toluene solution) (0.440 g, 2.00 mmol, 510 μL) was added dropwise. After that the mixture was stirred at rt for the appropriate time. Dichloromethane (20 mL) was added to the reaction mixture, then washed with saturated NaCl solution (3 × 10 mL), dried over anhydrous sodium sulfate, filtered, and evaporated. The crude residue was purified by column chromatography.

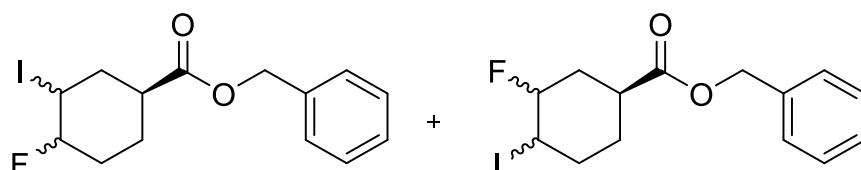
General procedure B for halofluorination reactions

Benzyl (*S**)-cyclohex-3-ene-1-carboxylate (216 mg, 1.00 mmol) and *N*-bromosuccinimide (0.178 g, 1.00 mmol) or *N*-iodosuccinimide (0.225 g, 1.00 mmol) were added to a 25 mL round-bottom flask fitted with a rubber septum, then the system was charged with argon. Dry dichloromethane (10 mL) was added under argon atmosphere, then Deoxo-Fluor (50 % toluene solution) (0.440 g, 2.00 mmol, 510 μL) was

added dropwise. The resulting mixture was stirred at rt for the appropriate time. Dichloromethane (20 mL) was added to the reaction mixture, then washed with saturated NaCl solution (3×10 mL), dried over anhydrous sodium sulfate, filtered, and evaporated. The crude residue was purified by column chromatography.

General procedure C for selenofluorination reactions

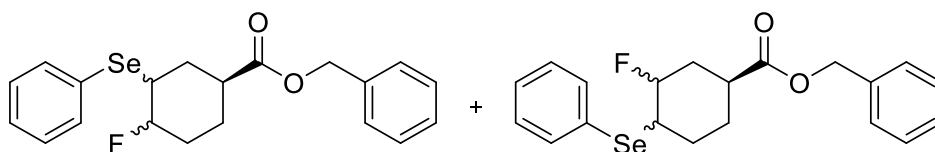
Benzyl cyclopent-3-ene-1-carboxylate (202 mg, 1.00 mmol) and phenylselenenyl bromide (0.236 g, 1.00 mmol) were added to a 25 mL round-bottom flask fitted with a rubber septum, then the system was charged with argon. Dry acetonitrile (10 mL) was added under argon atmosphere, then Deoxo-Fluor (50 % toluene solution) (0.440 g, 2.00 mmol, 510 μ L) was added dropwise. After that the mixture was stirred at rt for the appropriate time. Ethyl acetate (20 mL) was added to the re-



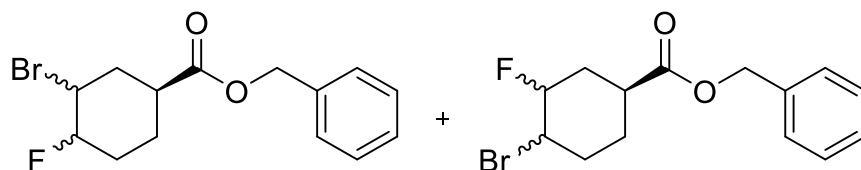
action mixture, then washed with saturated NaHCO_3 solution (3×10 mL), dried over anhydrous sodium sulfate, filtered, and evaporated. The crude residue was purified by column chromatography.

General procedure D for selenofluorination reactions

Benzyl cyclopent-3-ene-1-carboxylate (202 mg, 1.00 mmol) and phenylselenenyl bromide (0.236 g, 1.00 mmol) were added to a 25 mL round-bottom flask fitted with a rubber septum, then the system was charged with argon. Dry acetonitrile (10 mL) was added under argon atmosphere, then Deoxo-Fluor (50 % toluene solution) (0.440 g, 2.00 mmol, 510 μ L) was added dropwise. The resulting mixture was stirred at rt for the appropriate time. Ethyl acetate (20 mL) was added to the reaction mixture, then washed with saturated NaHCO_3 solution (3×10 mL), dried over anhydrous sodium sulfate, filtered, and evaporated. The crude residue was purified by column chromatography.



Benzyl (1*S,3*R**,4*R**)-3-bromo-4-fluorocyclohexane-1-carboxylate and benzyl (1*R*,3*R*,4*R*)-3-bromo-4-fluorocyclohexane-1-carboxylate (2aa) (mixture).**



Prepared according to *general procedure A* from benzyl (*S**)-cyclohex-3-ene-1-carboxylate, *N*-bromosuccinimide and Deoxo-Fluor for 6 h. Purification of the crude product by column chromatography on silica gel afforded the product mixture as a colorless oil (150 mg, 0.475 mmol, 48 %). R_f = 0.67 (hexane-ethyl acetate, 10:1). ^1H NMR (300 MHz, CDCl_3) δ 7.42 – 7.30 (m, 5H), 5.15 (d, J = 1.5 Hz, 2H), 5.02 – 4.57 (m, 1H), 4.45 – 4.19 (m, 1H), 2.93 – 2.71 (m, 1H), 2.54 – 1.79 (m, 6H); ^{13}C NMR (75 MHz, CDCl_3) δ 174.7, 136.4, 129.2, 128.9, 128.9, 128.7, 128.7, 91.9, 89.5, 67.1, 67.0, 48.8, 48.6, 48.4, 48.2, 38.3, 38.0, 37.9, 32.7, 29.5, 26.0, 24.1, 23.7; ^{19}F NMR (282 MHz, CDCl_3) δ –169.4, –170.0.

Benzyl (1*S,3*R**,4*R**)-3-iodo-4-fluorocyclohexane-1-carboxylate and benzyl (1*R*,3*R*,4*R*)-3-iodo-4-fluorocyclohexane-1-carboxylate (2ab) (mixture).**

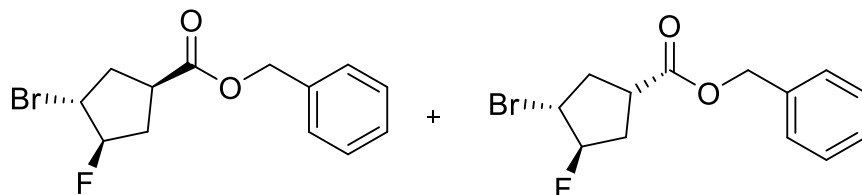
Prepared according to *general procedure B* from benzyl (*S**)-cyclohex-3-ene-1-carboxylate, *N*-iodosuccinimide and Deoxo-Fluor for 25 h. Purification of the crude product by column chromatography on silica gel afforded the product as a yellowish-brown oil (290 mg, 0.800 mmol, 80 %). R_f = 0.59 (hexane-ethyl acetate, 10:1). ^1H NMR (300 MHz, CDCl_3) δ 7.44 – 7.28 (m, 5H), 5.15 (d, J = 2.3 Hz, 2H), 5.07 – 4.67 (m, 1H), 4.46 (ddq, J = 26.7, 7.7, 4.3, 3.8 Hz, 1H), 2.81 (ddt, J = 13.2, 7.7, 4.1 Hz, 1H), 2.65 – 1.81 (m, 6H); ^{13}C NMR (75 MHz, CDCl_3) δ 174.4, 135.9, 128.6, 128.4, 128.33, 128.30, 128.11, 128.09, 92.5, 90.2, 74.9, 72.0, 66.6, 66.53, 66.49, 41.6, 40.6, 39.8, 39.2, 38.5, 35.7, 30.3, 29.1, 25.1, 24.9; ^{19}F NMR (282 MHz, CDCl_3) δ –162.5, –163.0.

Benzyl (1*S,3*R**,4*R**)-4-fluoro-3-(phenylselenanyl)cyclohexane-1-carboxylate and benzyl (1*R*,3*R*,4*R*)-4-fluoro-3-(phenylselenanyl)cyclohexane-1-carboxylate (2ac) (mixture).**

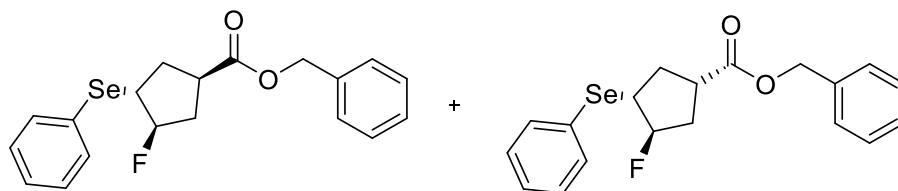
Prepared according to *general procedure D* from benzyl (*S**)-cyclohex-3-ene-1-carboxylate for 25 h. Purification of the crude product by column chromatography on silica gel afforded the product as a yellowish-brown oil (220 mg, 0.560 mmol, 56 %). R_f = 0.57 (hexane-ethyl

acetate, 10:1). ^1H NMR (300 MHz, CDCl_3) δ 7.71 – 7.19 (m, 10H), 5.21 – 5.06 (m, 2H), 3.80 – 3.42 (m, 1H), 2.79 (dq, $J = 9.2, 4.6$ Hz, 1H), 2.49 – 1.37 (m, 7H); ^{13}C NMR (75 MHz, CDCl_3) δ 175.5, 175.2, 134.4, 134.3, 129.7, 129.6, 129.0, 128.7, 128.6, 128.53, 128.48, 127.9, 75.7, 66.6, 39.5, 38.4, 30.7, 27.2, 25.7; ^{19}F NMR (282 MHz, CDCl_3) δ –149.4, –149.5.

Benzyl (1*S,3*R**,4*R**)-3-bromo-4-fluorocyclopentane-1-carboxylate and benzyl (1*R*,3*R*,4*R*)-3-bromo-4-fluorocyclopentane-1-carboxylate (2*ba*) (mixture).**

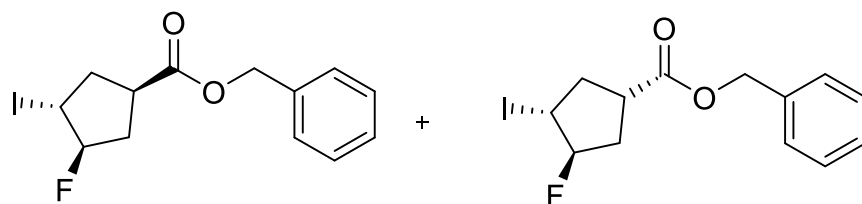


Prepared according to *general procedure B* from benzyl cyclopent-3-ene-1-carboxylate (202 mg, 1.00 mmol), *N*-bromosuccinimide and Deoxo-Fluor for 25 h. Purification of the crude product by column chromatography on silica gel afforded the product as a colorless oil (220



mg, 0.730 mmol, 73 %). $R_f = 0.62$ (hexane–ethyl acetate, 10:1). ^1H NMR (500 MHz, CDCl_3) δ 7.32–4.45 (m, 5H, Ar-H), 5.29 – 5.11 (m, 2H and 1H), 4.34 – 4.25 (m, 1H), 3.40 – 3.15 (m, 1H), 2.89 – 2.25 (m, 4H); ^{13}C NMR (75 MHz, CDCl_3) δ 176.2, 128.58, 128.57, 128.3, 128.2, 128.1, 97.6, 91.2, 66.9, 66.8, 52.0, 40.9, 40.7, 37.3, 37.1, 33.54, 33.45, 33.24, 33.17; ^{19}F NMR (282 MHz, CDCl_3) δ –162.3, –169.8.

Benzyl (1*S,3*R**,4*R**)-3-iodo-4-fluorocyclopentane-1-carboxylate and benzyl (1*R*,3*R*,4*R*)-3-iodo-4-fluorocyclopentane-1-carboxylate (2*bb*) (mixture).**



Prepared according to the *general procedure A* from benzyl cyclopent-3-ene-1-carboxylate (202 mg, 1.00 mmol), *N*-iodosuccinimide and Deoxo-Fluor for 24 h. Purification of the crude product by column chromatography on silica gel afforded the product as a brown oil (330 mg, 0.950 mmol, 95 %). $R_f = 0.60$ (hexane–ethyl acetate, 10:1). ^1H NMR (300 MHz, CDCl_3) δ 7.42 – 7.27 (m, 5H), 5.41 – 5.18 (m, 1H), 5.16 (d, $J = 3.7$ Hz, 2H), 4.49 – 4.19 (m, 1H), 3.45 – 3.04 (m, 1H), 2.95 – 2.20 (m, 4H); ^{13}C NMR (75 MHz, CDCl_3) δ 173.9, 135.8, 128.6, 128.34, 128.25, 128.2, 103.0, 101.8, 100.5, 99.4, 66.9, 66.8, 41.5, 41.4, 39.2, 38.70, 33.69, 33.6, 33.4, 33.3, 28.1, 27.8, 23.8, 23.5; ^{19}F NMR (282 MHz,

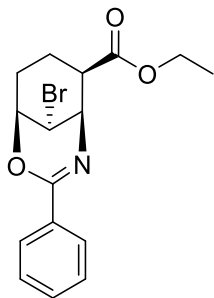
CDCl_3) δ –150.5, –160.0.

Benzyl (1*S,3*R**,4*R**)-4-fluoro-3-(phenylselanyl)cyclopentane-1-carboxylate and benzyl (1*R*,3*R*,4*R*)-4-fluoro-3-(phenylselanyl)cyclopentane-1-carboxylate (2*bc*) (mixture).**

Prepared according to *general procedure C* from benzyl cyclopent-3-ene-1-carboxylate (202 mg, 1.00 mmol) for 4 h. Purification of the crude product by column chromatography on silica gel afforded the product as a yellow oil (170 mg, 0.450 mmol, 45 %). $R_f = 0.37$ (hexane–ethyl acetate, 10:1). ^1H NMR (300 MHz, CDCl_3) δ 7.55 (dt, $J = 6.6, 2.6$ Hz, 2H), 7.44 – 7.26 (m, 8H), 5.16 (s, 2H), 5.13 – 4.90 (m, 1H), 3.98 – 3.69 (m, 1H), 3.25 – 3.10 (m, 1H), 2.77 – 1.98 (m, 4H); ^{13}C NMR (75 MHz, CDCl_3) δ 174.9, 136.4, 134.6, 134.2, 129.92, 129.87, 129.1, 128.9, 128.8, 128.71, 128.67, 128.5, 128.4, 102.0, 100.7, 99.6, 98.3, 67.2, 46.8, 46.6, 45.3, 45.0, 42.2, 42.1, 35.8, 35.5, 35.4, 35.1, 34.6, 34.2; ^{19}F

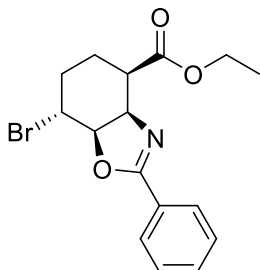
NMR (282 MHz, CDCl_3) δ –159.9, –163.0.

Ethyl (1*S**,5*R**,6*R**,9*S**)-9-bromo-3-phenyl-2-oxa-4-azabicyclo[3.3.1]non-3-ene-6-carboxylate (**2ca'**).



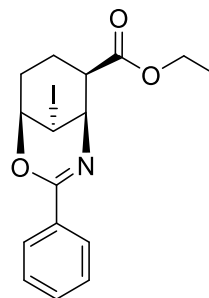
Prepared according to *general procedure A* from ethyl (1*R**,2*S**)-2-benzamidocyclohex-3-ene-1-carboxylate (273 mg, 1.00 mmol), *N*-bromosuccinimide and Deoxo-Fluor for 3 h. Purification of the crude product by column chromatography on silica gel afforded the product as a yellowish solid (50.0 mg, 0.142 mmol, 13 %). R_f = 0.44 (hexane–ethyl acetate, 7:1). Mp 90 °C. ^1H NMR (500 MHz, CDCl_3) δ 7.94 – 7.89 (m, 2H), 7.50 – 7.43 (m, 1H), 7.38 (t, J = 7.6 Hz, 2H), 4.71 (tt, J = 3.9, 2.2 Hz, 1H), 4.64 (td, J = 3.8, 1.4 Hz, 1H), 4.47 (q, J = 2.9 Hz, 1H), 4.25 (qd, J = 7.1, 2.5 Hz, 2H), 3.36 (ddd, J = 12.4, 4.7, 2.8 Hz, 1H), 2.39 (dddd, J = 15.4, 13.6, 5.7, 2.1 Hz, 1H), 2.16 – 2.10 (m, 1H), 1.86 (ddd, J = 10.4, 8.7, 4.4 Hz, 1H), 1.77 (qd, J = 14.5, 13.8, 5.2 Hz, 1H), 1.33 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 172.8, 157.5, 131.9, 131.1, 128.1, 127.6, 73.3, 60.8, 54.2, 46.0, 41.5, 26.4, 17.2, 14.3; HRMS calcd. for $\text{C}_{16}\text{H}_{19}\text{BrNO}_3^+$ ($[\text{M} + \text{H}]^+$): 352.0470. Found: 352.0550.

Ethyl (3*aR**,4*R**,7*R**,7*aR**)-7-bromo-2-phenyl-3*a*,4,5,6,7,7*a*-hexahydrobenzo[d]oxazole-4-carboxylate (**2ca''**).



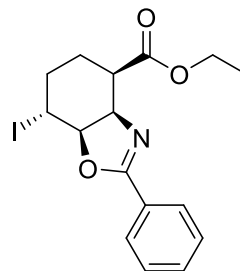
Prepared according to *general procedure A* from ethyl (1*R**,2*S**)-2-benzamidocyclohex-3-ene-1-carboxylate (273 mg, 1.00 mmol), *N*-bromosuccinimide and Deoxo-Fluor for 3 h. Purification of the crude product by column chromatography on silica gel afforded the product as a white solid (170 mg, 0.480 mmol, 48 %). R_f = 0.34 (hexane–ethyl acetate, 7:1). Mp 117 °C. ^1H NMR (500 MHz, CDCl_3) δ 8.02 – 7.97 (m, 2H), 7.55 – 7.48 (m, 1H), 7.42 (t, J = 7.6 Hz, 2H), 5.01 (dd, J = 8.4, 6.7 Hz, 1H), 4.73 (dd, J = 8.3, 5.2 Hz, 1H), 4.30 (qd, J = 7.1, 4.5 Hz, 2H), 4.03 – 3.94 (m, 1H), 3.13 – 3.04 (m, 1H), 2.25 (dq, J = 12.3, 4.1, 3.4 Hz, 1H), 1.98 (dt, J = 13.3, 4.8 Hz, 1H), 1.93 – 1.77 (m, 2H), 1.34 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 175.1, 167.2, 134.6, 131.4, 131.2, 130.3, 86.6, 69.5, 63.7, 52.9, 44.2, 32.8, 24.4, 17.2; HRMS calcd. for $\text{C}_{16}\text{H}_{19}\text{BrNO}_3^+$ ($[\text{M} + \text{H}]^+$): 352.0470. Found: 352.0544.

Ethyl (1*S**,5*R**,6*R**,9*S**)-9-iodo-3-phenyl-2-oxa-4-azabicyclo[3.3.1]non-3-ene-6-carboxylate (**2cb'**).



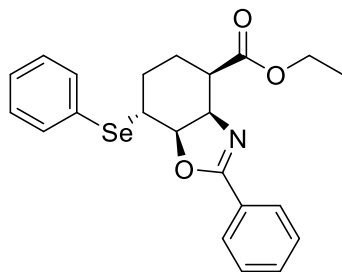
Prepared according to *general procedure A* from ethyl (1*R**,2*S**)-2-benzamidocyclohex-3-ene-1-carboxylate (273 mg, 1.00 mmol), *N*-iodosuccinimide and Deoxo-Fluor for 2 h. Purification of the crude product by column chromatography on silica gel afforded the product as a yellowish solid (34.0 mg, 0.085 mmol, 9 %). R_f = 0.32 (hexane–ethyl acetate, 7:1). Mp 90 °C. ^1H NMR (500 MHz, CDCl_3) δ 8.01 – 7.75 (m, 2H), 7.49 – 7.34 (m, 3H), 4.85 – 4.79 (m, 1H), 4.74 – 4.69 (m, 1H), 4.43 – 4.38 (m, 1H), 4.25 (ddq, J = 11.2, 7.1, 3.9 Hz, 2H), 3.39 (ddd, J = 11.8, 5.2, 2.7 Hz, 1H), 2.58 – 2.47 (m, 1H), 2.23 – 2.19 (m, 1H), 1.86 – 1.76 (m, 2H), 1.33 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 174.5, 158.4, 132.4, 129.5, 129.0, 128.7, 75.5, 62.3, 56.4, 44.5, 29.0, 27.4, 19.2, 15.8; HRMS calcd. for $\text{C}_{16}\text{H}_{19}\text{INO}_3^+$ ($[\text{M} + \text{H}]^+$): 400.0410. Found: 400.0405.

Ethyl (3*aR**,4*R**,7*R**,7*aR**)-7-iodo-2-phenyl-3*a*,4,5,6,7,7*a*-hexahydrobenzo[d]oxazole-4-carboxylate (**2cb''**).



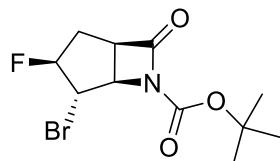
Prepared according to *general procedure A* from ethyl (1*R**,2*S**)-2-benzamidocyclohex-3-ene-1-carboxylate (273 mg, 1.00 mmol), *N*-iodosuccinimide and Deoxo-Fluor for 2 h. Purification of the crude product by column chromatography on silica gel afforded the product as a yellowish solid (180 mg, 0.450 mmol, 40 %). R_f = 0.24 (hexane–ethyl acetate 7:1), Mp 105 °C. ^1H NMR (500 MHz, CDCl_3) δ 8.01 – 7.95 (m, 2H), 7.51 (t, J = 7.4 Hz, 1H), 7.42 (t, J = 7.6 Hz, 1H), 5.12 (t, J = 7.8 Hz, 1H), 4.58 (dd, J = 8.1, 5.5 Hz, 1H), 4.35 – 4.24 (m, 2H), 4.01 (ddd, J = 11.5, 7.4, 4.5 Hz, 1H), 3.09 (dt, J = 12.3, 5.3 Hz, 1H), 2.30 (dq, J = 13.8, 4.5 Hz, 1H), 2.00 – 1.74 (m, 3H), 1.34 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 172.2, 164.3, 131.9, 131.8, 128.61, 128.56, 128.31, 128.30, 127.3, 85.44, 85.38, 66.3, 66.1, 60.9, 60.8, 41.4, 41.3, 32.10, 32.05, 26.5, 26.3, 23.23, 23.20, 14.27; HRMS calcd. for $\text{C}_{16}\text{H}_{19}\text{INO}_3^+$ ($[\text{M} + \text{H}]^+$): 400.0410. Found: 400.0401.

Ethyl (3aR*,4R*,7R*,7aR*)-2-phenyl-7-(phenylselanyl)-3a,4,5,6,7,7a-hexahydrobenzo[d]oxazole-4-carboxylate (2 cc”).



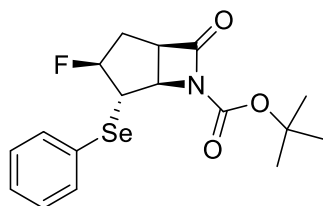
Prepared according to *general procedure C* from ethyl (1R*,2S*)-2-benzamidocyclohex-3-ene-1-carboxylate (273 mg, 1.00 mmol) for 3 h. Purification of the crude product by column chromatography on silica gel afforded the product as a white solid (155 mg, 0.361 mmol, 33 %). $R_f = 0.34$ (hexane–ethyl acetate 7:1), Mp 133 °C. ^1H NMR (300 MHz, CDCl_3) δ 7.84 (d, $J = 7.3$ Hz, 2H), 7.65 (dt, $J = 6.4, 1.6$ Hz, 2H), 7.48 (t, $J = 7.4$ Hz, 1H), 7.42–7.27 (m, 5H), 4.91 (t, $J = 7.8$ Hz, 1H), 4.68 (dd, $J = 8.0, 5.4$ Hz, 1H), 4.27 (q, $J = 7.1$ Hz, 2H), 3.18 (ddd, $J = 10.4, 7.2, 4.8$ Hz, 1H), 2.92 (dt, $J = 12.0, 4.9$ Hz, 1H), 2.12 (dq, $J = 14.0, 4.5$ Hz, 1H), 1.99–1.85 (m, 1H), 1.78 (ddd, $J = 15.5, 7.6, 3.6$ Hz, 1H), 1.58–1.47 (m, 1H), 1.31 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 172.5, 153.5, 135.8, 131.5, 129.2, 128.5, 128.1, 82.9, 66.1, 60.7, 42.8, 42.1, 27.2, 21.9, 14.3; HRMS calcd. for $\text{C}_{22}\text{H}_{24}\text{INO}_3\text{Se}^+$ ($[\text{M} + \text{H}]^+$): 430.0921. Found: 430.0916.

Tert-butyl (1R*,3S*,4S*,5R*)-4-bromo-3-fluoro-7-oxo-6-azabicyclo[3.2.0]heptane-6-carboxylate (2da).



Prepared according to *general procedure A* from *tert*-butyl (1R*,5S*)-7-oxo-6-azabicyclo[3.2.0]hept-3-ene-6-carboxylate (418 mg, 2.00 mmol), *N*-bromosuccinimide and Deoxo-Fluor for 26 h. Purification of the crude product by column chromatography on silica gel afforded the product as a white solid (180 mg, 0.586 mmol, 29 %). $R_f = 0.31$ (hexane–ethyl acetate, 5:1). Mp 107 °C. ^1H NMR (300 MHz, CDCl_3) δ 5.33 (dd, $J = 49.8, 2.4$ Hz, 1H), 4.72–4.64 (m, 1H), 4.58 (dd, $J = 4.3, 1.4$ Hz, 1H), 3.82–3.71 (m, 1H), 2.72–2.32 (m, 2H), 1.53 (d, $J = 4.2$ Hz, 9H); ^{13}C NMR (75 MHz, CDCl_3) δ 178.1, 150.9, 101.7, 99.3, 84.6, 62.6, 53.5, 47.3, 47.0, 31.3, 31.0, 28.6; ^{19}F NMR (282 MHz, CDCl_3) δ –158.9; HRMS calcd. for $\text{C}_{16}\text{H}_{19}\text{BrNO}_3\text{Na}^+$ ($[\text{M} + \text{Na}]^+$): 330.1474. Found: 330.0117.

Tert-butyl (1R,3S,4S,5R)-3-fluoro-7-oxo-4-(phenylselanyl)-6-azabicyclo[3.2.0]heptane-6-carboxylate (2dc).



Prepared according to *general procedure D* from *tert*-butyl 7-oxo-6-azabicyclo[3.2.0]hept-3-ene-6-carboxylate 209 mg (1 mmol) for 25 h. Purification of the crude product by column chromatography on silica gel afforded the product as a yellow oil (280 mg, 0.727 mmol, 73 %). $R_f = 0.50$ (hexane–ethyl acetate, 4:1). ^1H NMR (300 MHz, CDCl_3) δ 7.72–7.51 (m, 2H), 7.41–7.20 (m, 3H), 5.41–5.05 (m, 1H), 4.72–4.37 (m, 1H), 4.22 (d, $J = 16.7$ Hz, 1H), 3.93–3.57 (m, 1H), 2.60–2.38 (m, 1H),

2.21 (dddd, $J = 42.1, 15.4, 9.1, 3.9$ Hz, 1H), 1.56–1.43 (m, 9H); ^{13}C NMR (75 MHz, CDCl_3) δ 182.21, 155.07, 134.76, 130.22, 129.09, 127.52, 101.58, 99.16, 84.02, 61.65, 53.55, 45.08, 44.85, 32.69, 32.41, 28.62; ^{19}F NMR (282 MHz, CDCl_3) δ –158.5; HRMS calcd. for $\text{C}_{17}\text{H}_{20}\text{FNO}_3\text{SeNa}^+$ ($[\text{M} + \text{Na}]^+$): 408.0490. Found: 408.0485.

CRedit authorship contribution statement

Tamás T. Novák: . Klára Aradi: Methodology. Ágnes Gömöry: . Melinda Nonn: Supervision. Gábor Hornyánszky: Writing – original draft, Visualization. Loránd Kiss: .

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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