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Studies on fluorinative difunctionalization of some β-amino acid derivatives and β-lactams with a cycloalkene framework

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ABSTRACT

Studies on the arylfluorination of some *β*-lactams and *β*-amino esters with a cyclooctene framework were performed under various experimental conditions with emphasis on the type of the fluorinating agents and the palladium catalysts. The arylfluorinative difunctionalization of cyclooctene-fused *β*-lactam, performed with phenylboronic acid, in the presence of several electrophilic fluorinating agents [1-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate, 1-fluoropyridinium triflate, *N*-fluorobenzensulfonimide) and palladium catalyst (*bis*(dibenzylideneacetone)palladium(0), *bis*(acetonitrile)dichloropalladium(II), *bis*(triphenylphosphine) palladium(II) dichloride, palladium(II) chloride], azacyclic ligands, and solvents, gave a separable mixture of five fluorinated and non-fluorinated products. Arylfluorination of cyclooctane-*β*-amino esters when performed under similar conditions proceeded with full regio- and stereoselective manners affording phenyl-fluorinated compounds. Possible synthetic routes related to the outcome of these types of olefin bond difunctionalizations are also presented.

1. Introduction

Fluorine plays an important role in modern medicinal chemistry and drug design, because of its unique properties such as high electronegativity ($\chi = 3.98$), exceptional strength of the C–F bond (≈441 kJ·mol^{-1}), and a compact van der Waals radius (1.47 Å) [1]. The common strategy involves the transformation of a C–H unit with a C–F moiety in an organic scaffold. This often results in significant changes to physicochemical and biological properties, including polar hydrophobicity, lipophilicity, polarity, acid-base characteristics, and metabolic stability, without markedly altering molecular size or shape. This capacity to fine-tune key properties without a significant geometric penalty has led to the pervasive incorporation of fluorine, which is now present in 20–30% of all marketed drugs [2].

Given these advantages, the synthesis of fluorinated scaffolds has become an active area of research in synthetic organic chemistry, with strategies ranging from direct fluorination using elemental fluorine or specialized reagents, as well as indirect approaches involving the use of fluorinated building blocks or functional groups [3]. Recent advances now include electrophilic, nucleophilic, and radical fluorination, offering site-selective and functional-group-tolerant methods [4–6].

Among the emerging strategies, transition-metal-catalyzed fluorofunctionalizations have gained significant attention for their efficiency and versatility. In particular, Pd-catalyzed arylfluorination of

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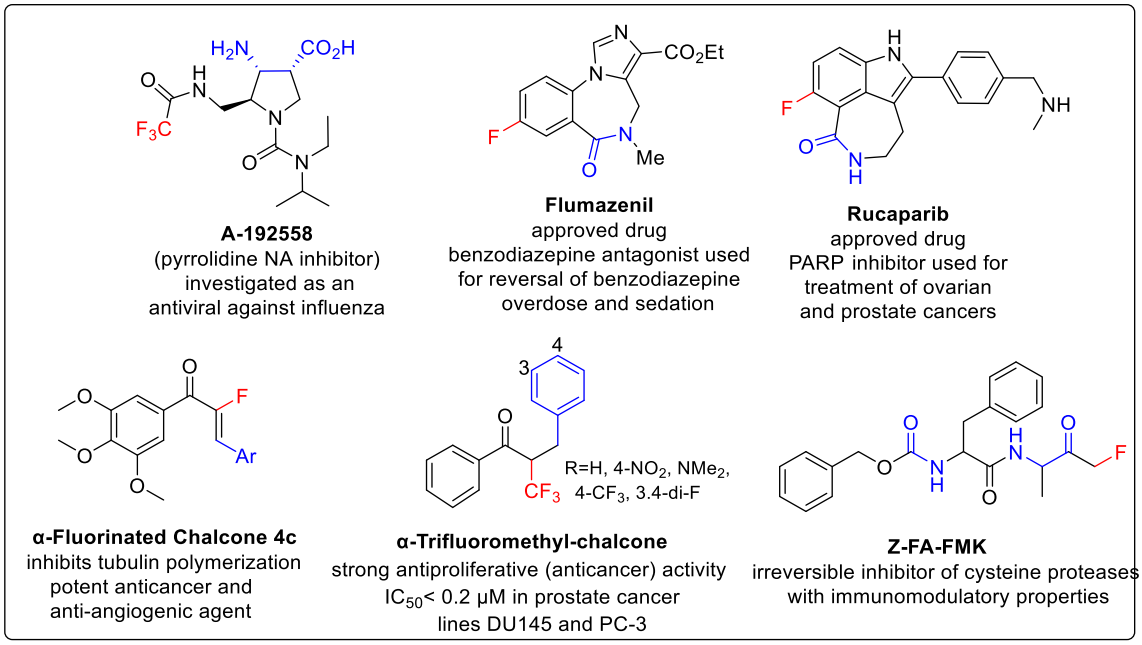


Fig. 1. Fluorinated scaffolds in natural products, bioactive compounds and approved drugs.

alkenes represents a powerful difunctionalization strategy that allows simultaneous incorporation of an aryl group and a fluorine atom across a C–C double bond, addressing two major goals of modern synthetic methodology [3k, 7–11].

Within this context, α-fluoro-(β or γ)-aryl motifs with cyclic amino acids derivatives represent an emerging class of biological and pharmaceutical interest. These frameworks combine the strong electronic effects of an α-fluorine atom, which enhances metabolic stability, acidity, and conformational preferences, with the presence of (β or γ)-aryl groups contributing to improved receptor binding via π–π interactions, creating unique physicochemical profiles. This can be exemplified with α-fluorinated chalcone 4c, which inhibits tubulin polymerization and displays potent anticancer and anti-angiogenic activity. In a similar manner, α-trifluoromethyl-chalcones exhibit remarkable antiproliferative properties, with submicromolar efficacy ($IC_{50} < 0.2$ μM) in prostate cancer cell lines DU145 and PC-3. Beyond oncology, fluorine-containing β-cyclic amino acid agents, such as pyrrolidine-based neuraminidase inhibitor A-192,558, have been investigated as antivirals against influenza. An additional example is Rucaparib, a PARP inhibitor drug approved for ovarian and prostate cancers as illustrated in Fig. 1 [12–18]. Collectively, these cases underscore the growing importance of the synthesis of complex fluorinated motifs, which serve both as therapeutic candidates and direct drug candidates.

β-Lactams are structural motifs of outstanding interest in medicinal chemistry and pharmaceutical research due to their wide range of biological properties, in particular, antibacterial activities. Therefore, the design and preparation of various β-lactam frameworks with biological potential exerts a high interest among organic and medicinal chemists [19].

Conformationally rigid cyclic amino acid derivatives possess a wide range of biological and pharmaceutical properties. Some small-molecular representatives are known as antifungal or antiviral agents and antibiotics or they are elements in various pharmacologically important bioactive products (anticancer agents, antineuralgics, cardioprotective or anti-inflammatory agents). In addition, they function as building blocks in peptide chemistry. Conformationally restricted or non-canonical cyclic amino acids with either an aryl moiety or a fluorine-containing element in their structure may be regarded as interesting structural motifs in foldamer chemistry, because of their influence on the secondary structures of peptides [20].

Earlier, our group applied Pd-catalyzed olefin arylfluorination of easily accessible strained cyclooct-4-ene β-amino esters and cyclooctene-fused azetidinones to obtain various fluorinated scaffolds in a fully regio- and stereocontrolled fashion [21a].

This novel synthetic approach is particularly noteworthy and opens new avenues for the synthesis of diverse and structurally intricate α-fluoro-γ-aryl cyclic amino acid derivatives, paving the way for potential applications in pharmaceutical and medicinal chemistry.

2. Results and discussion

The aim of the present work is to study the arylfluorination protocol and investigate a range of palladium catalysts [Pd(0) or Pd(II)), including $Pd(dba)_2$, $PdCl_2(CH_3CN)_2$, $PdCl_2(PPh_3)_2$, and $PdCl_2$], in combination with different electrophilic fluorinating agents as depicted in Fig. 2. These systems were examined under varying reaction conditions (reaction time, temperature, solvent, and additives), in order to establish the optimal protocol. Subsequently, to demonstrate the

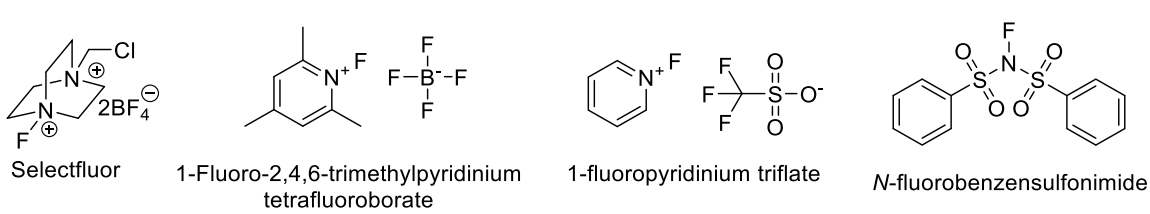
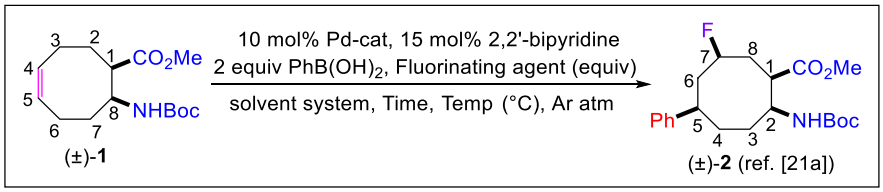


Fig. 2. Some electrophilic fluorinating agents used in this work.

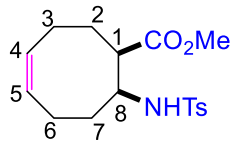
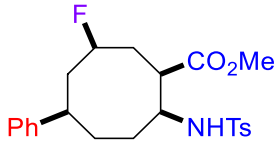
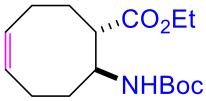
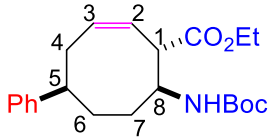
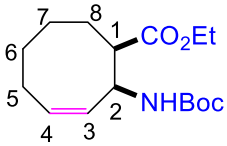
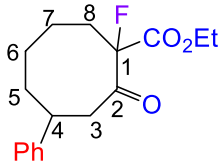
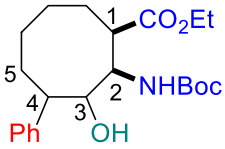
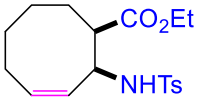
Table 1
Investigation of the reaction conditions on the phenylfluorination of cyclooctene β-amino ester (±)-**1**; optimization of the reaction conditions.



Entry	Catalyst (10 mol%)	Fluorinating agent (equiv)	time (h)	Temp (°C)	Solvent (ratio)	Additive	Yield (%)
1	$PdCl_2$	Selectfluor (2.0)	23	RT	DCM/MeCN/MeOH (8:5:1)	—	5–6
2	$Pd(dba)_2$	Selectfluor (2.0)	5	RT	DCM/MeCN/MeOH (8:5:1)	—	13
3	$(Ph_3P)_2PdCl_2$	Selectfluor (2.0)	3	RT	DCM/MeCN/MeOH (8:5:1)	—	13
4	$Pd(OAc)_2$	Selectfluor (2.0)	23	RT	DCM/MeCN/MeOH (8:5:1)	BMIM-BF_4 (1 g)	—
5	$PdCl_2(CH_3CN)_2$	Selectfluor (2.0)	2	RT	DCM/MeCN/MeOH (8:5:1)	—	33
6	$PdCl_2(CH_3CN)_2$	NFSI (2.0)	23	40 °C	DCM/MeCN/MeOH (8:5:1)	—	3
7	$PdCl_2(CH_3CN)_2$	trimethyl-1-F-pyridinium-BF_4 (2.0)	23	RT	DCM/MeCN/MeOH (8:5:1)	—	—
8	$PdCl_2(CH_3CN)_2$	1-F-pyridinium-OTf (2.0)	23	RT	DCM/MeCN/MeOH (8:5:1)	—	—
9	$PdCl_2(CH_3CN)_2$	Xtal-Fluor-E (2.0)	23	RT	DCM	—	—
10	$PdCl_2(CH_3CN)_2$	Deoxo-Fluor (4.0)	23	RT	DCM	—	—
11	$PdCl_2(CH_3CN)_2$	KF (2.0)	23	40 °C	DCM/MeCN/MeOH (8:5:1)	10 mol% Kryptofix	—
12	$PdCl_2(CH_3CN)_2$	KF (2.0)	23	reflux	MeCN	1.0 eq 18-Crown-6	—
13	SPhos-Pd-G4	Selectfluor (2.0)	23	RT to 40 °C	DCM/MeCN/MeOH (8:5:1)		28

Note: SPhos-Pd-G4: Methanesulfonato(2-dicyclohexylphosphino-2′,6′-dimethoxy-1,1′-biphenyl)(2′-methylamino-1,1′-biphenyl-2-yl)palladium(II); $Pd(dba)_2$: *bis* (dibenzylidene-acetone)palladium(0).

Table 2
Phenylfluorination of cyclooctene β-amino esters.

Entry	Cyclooctene β-amino esters	Product	time (h)	Yield (%)
1	 (±)-**3**	 ref. [21a] (±)-**6**	23 h	29%
2	 (±)-**4**	 (±)-**7**	2 h	13%
3	 (±)-**5**	 (±)-**8**  (±)-**9**	3.5 h	(±)-**8:** 11% (±)-**9:** 20%
4	 (±)-**10**	mostly starting compound or unidentifiable polymeric material	60	-

Standard conditions: $PdCl_2(CH_3CN)_2$ (10 mol%) in the presence of 2,2′-bipyridyl (15 mol%), $PhB(OH)_2$ (2 equiv), and Selectfluor (2 equiv) in CH_2Cl_2/MeCN/MeOH (8:5:1) at room temperature under Ar.

versatility and reliability of the method, we applied it for the synthesis of several model compounds, ring systems, including cyclooctene β-amino esters, β-lactams, five- and six-membered β-amino esters, enabling access to structurally diverse fluorinated scaffolds of potential synthetic

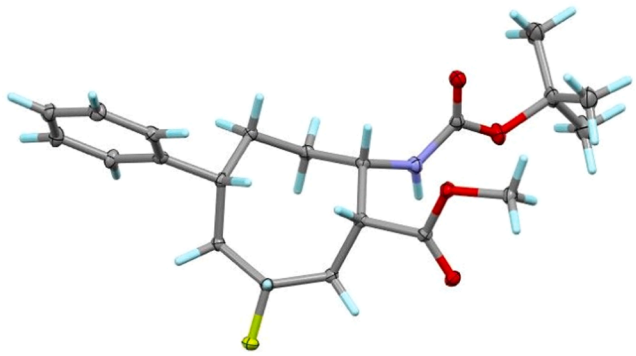


Fig. 3. Single crystal X-ray structure of fluorine-containing amino ester (±)-**2**. The ORTEP style representation was displayed at a 30% probability level for better clarity.

value (Scheme 2).

At the outset, we selected racemic amino ester (±)-**1** as the model compound for the reaction condition studies for arylfluorination. The screening results are summarized in Table 1. Initially, substrate (±)-**1** was treated with Selectfluor (2.0 equiv) in the presence of $PdCl_2$ (10 mol %), 2,2′-bipyridyl (15 mol%) as ligand, and $PhB(OH)_2$ (2.0 equiv) in DCM/MeCN/MeOH (8:5:1) at room temperature for 23 h, affording the desired fluorinated product with low conversion in a poor isolated yield of only 5–6% (Table 1, entry 1). Note that the selection of the solvent system was based on earlier published literature data [21].

To study the effect of the palladium source, a variety of Pd catalysts were evaluated (Table 1, entries 1–5). Among them, both *bis*-dibenzydileneacetone-Pd(0) and *bis*-(triphenylphosphine)$PdCl_2$ afforded the desired fluorinated product (±)-**2** in 13% yield (Table 2, entries 2 and 3, Fig. 3). Taking into consideration the original reaction conditions (Scheme 1a.), when $Pd(OAc)_2$ was used as the Pd source, the reaction failed in the ionic liquid 1-butyl-3-methyl imidazolium hexafluorophosphate (entry 4). The $PdCl_2(MeCN)_2$/Selectfluor combination, in turn, reached a yield of 33% in a shorter reaction time (2 h) (entry 5).

Further screening of alternative electrophilic fluorinating agents (NFSI, pyridinium-F salts) and attempts with nucleophilic reagents such as Xtal-Fluor-E, Deoxo-Fluor, KF protocols (with Kryptofix or 18-crown-6/*t*-BuOH) either failed to furnish isolable products or were not productive under the tested conditions (entries 6–12).

It should be noted that by using SPhos-Pd-G4 catalyst with Selectfluor in DCM/MeCN/MeOH solvent system an isolated yield of 28% of compound (±)-**2** could be attained (entry 13).

The solvent mixture DCM/MeCN/MeOH (8:5:1) at RT was retained as the preferred solvent system. Thus, the best reaction conditions were found as follows: *bis*-acetonitrile-$PdCl_2$ (10 mol%) with Selectfluor (2.0 equiv) in DCM/MeCN/MeOH (8:5:1) at room temperature for 2 h (Table 1, entry 5). The structure of phenylfluorinated amino ester (±)-**2** could also be clarified by X-ray investigations (Fig. 3 and supplementary material).

After studying various reaction conditions, the next goal was to investigate the scope and limitations of the reaction. To this end, we tested the protocol efficiency using first some eight-membered ring systems, such as various cyclooctene β-amino esters as detailed in Table 2. First, *cis N*-tosyl-protected amino ester (±)-**3** was subjected to phenylfluorination, affording selectively the single arylfluorinated product (±)-**6** in 29% yield (Table 2, entry 1, Fig. 4, and see also ref 21) with the fluorine atom located at C-7 and the phenyl substituents on the C-5 atom. In contrast, *trans* β-amino ester (±)-**4** yielded only phenylated product (±)-**7** in a lower isolated yield of 13% (entry 2). The relative orientation of the pH ring, connected to C-5 of the eight-membered ring, has been certified by NOESY experiments and the phenyl and ester groups were found to be in a *trans*-relative arrangement (Fig. 5). Next, arylfluorination of amino ester (±)-**5** under similar conditions delivered two separable products: the novel phenyl-fluorinated scaffold (±)-**8** and a difunctionalized amino ester derivative (±)-**9**, which were separated and isolated by means of column chromatography in 11% and 20% yields, respectively (entry 3). The formation of hydroxylated compound (±)-**9** might be the result of the aqueous workup of the reaction mixture. Elucidation of the structure of these two products was attempted by 2D NMR analysis. Compound (±)-**8** was found to contain the fluorine atom at the C-1 position, while the pH ring is connected to C-4 of the cyclooctene skeleton. Unfortunately, the orientation of these groups could not be determined. In the case of product (±)-**9**, the pH and the hydroxy groups are located at the C-4 and C-3 atoms of the cyclooctane framework. Unfortunately, contrary to all our efforts, the determination of their relative steric arrangement was not successful.

Finally, it should be noted that in contrast to the behavior of (±)-**2**, compound (±)-**10**, the Ts-protected analogue of (±)-**5**, failed to yield any well-defined product, even after prolonged (60 h) reaction time (entry 4).

Although product (±)-**8** was formed in modest isolated yield,

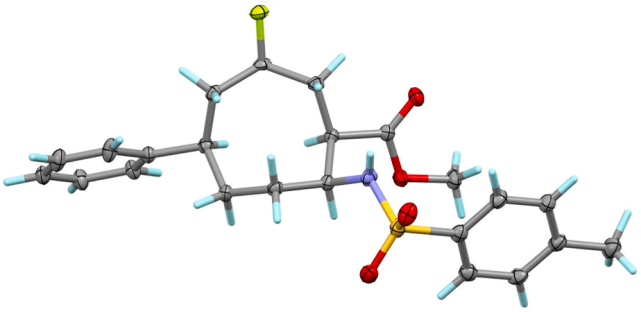


Fig. 4. Single crystal X-ray structure of fluorine-containing amino ester (±)-**6**. The ORTEP style representation was displayed at a 30% probability level for better clarity.

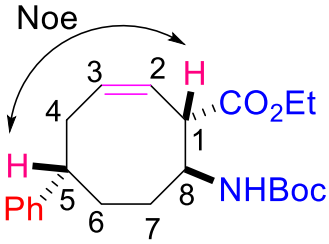
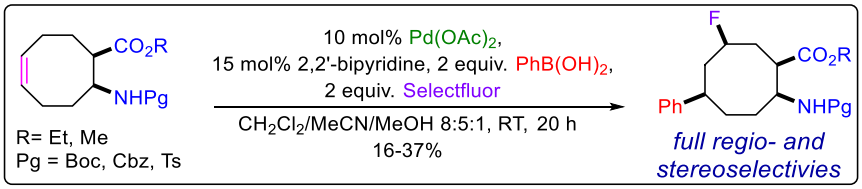


Fig. 5. NOE-correlation between H-1 and H-5 in compound (±)-**7**.



Scheme 1a. Earlier work: synthesis of fluorinated scaffolds via phenylfluorination of cyclooct-4-ene β-amino esters [21a].

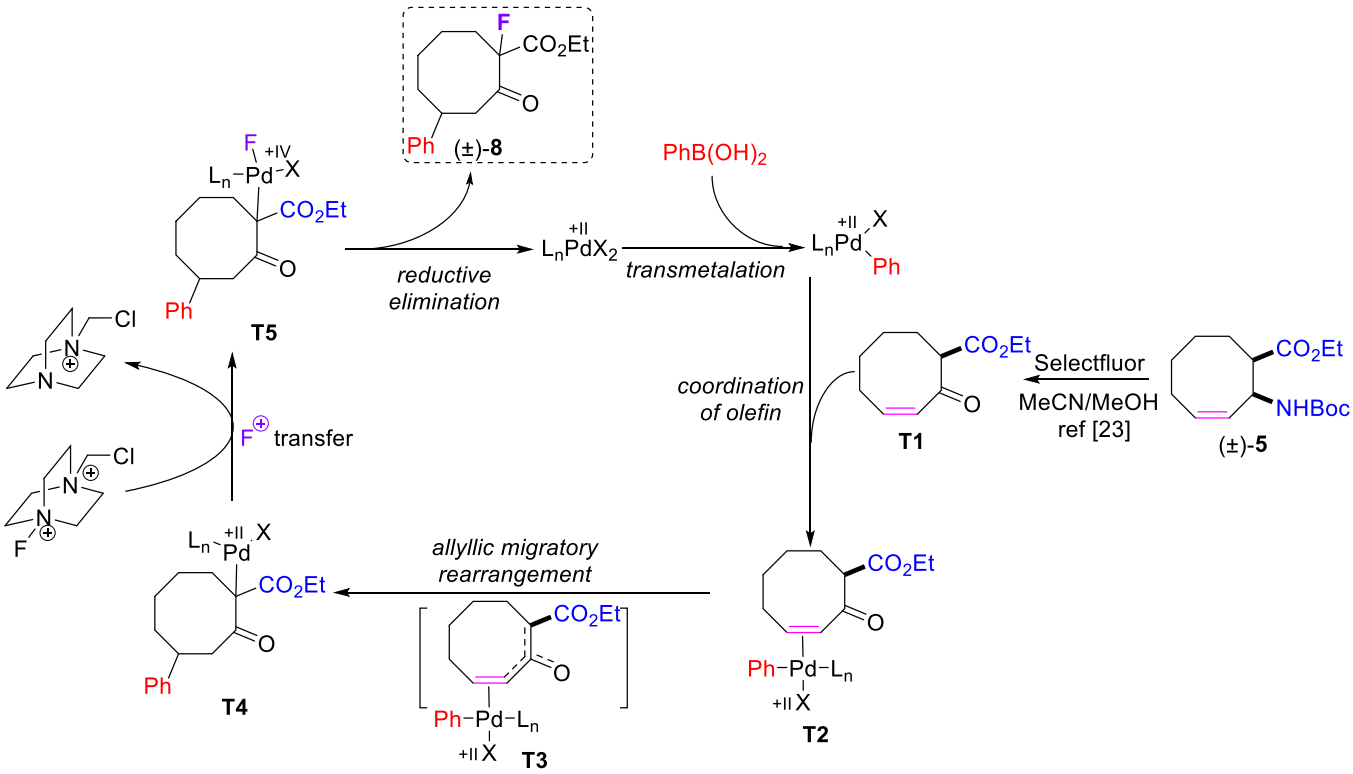
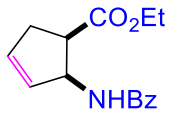
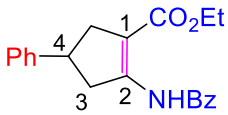
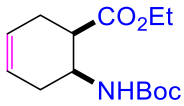
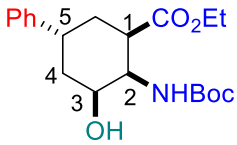


Fig. 6. Proposed synthetic pathway for the formation of compound (±)-**8**.

Table 3
Phenylfluorination of five- and six-membered β-amino esters.

Entry	Five- and six-membered cyclic β-amino esters	Product	time (h)	yield (%)
1	 (±)-**11**	 ref [22]. (±)-**13**	48 h	20%[a] 24%[b]
2	 (±)-**12**	 (±)-**14**	48 h	19%[a] 16%[c] 22%[d]

[a] Conditions: $PdCl_2(CH_3CN)_2$ (10 mol%) in the presence of 2,2′-bipyridyl (15 mol%), $PhB(OH)_2$ (2 equiv), and Selectfluor (2 equiv) in CH_2Cl_2/MeCN/MeOH (8:5:1) at RT under Ar.
[b] 40 °C was used instead of RT.
[c] Using $Pd(OAc)_2$ (10 mol%) instead of $PdCl_2(CH_3CN)_2$.
[d] Using CH_2Cl_2/MeOH (4:1) instead of CH_2Cl_2/MeCN/MeOH (8:5:1).
Note that taking into account that Selectfluor is well soluble in polar protic solvents (MeOH), while its reactivity is favored in polar aprotic solvents (MeCN), while the substrates used in this work a highly soluble in CH_2Cl_2 in some cases, although not always, this type of three-component system was superior compared with two-component systems.

apparently its formation seemed to be somehow surprising and curious. The proposed pathway for the formation of fluorinated compounds (±)-**8** is illustrated in Fig. 6. In the first step, oxidative deamination of *N*-Boc-protected amine (±)-**5** using Selectfluor [23] leads to carbonyl intermediate **T1**. Subsequently, coordination of the transmetalated species to the ring olefin bond in **T1** forms intermediate **T2**, which undergoes selective allylic migratory insertion across **T3** to give species **T4**. This latter intermediate leads to fluorinated target product (±)-**8** through fluoronium transfer and reductive elimination (Fig. 6).

In continuation, we have selected two representative amino esters analogs, the five- and six-membered cycloalkene β-amino esters, which were subjected to phenylfluorination. *N*-Benzoyl-protected cyclopentene β-amino ester (±)-**11** afforded phenyl-substituted product (±)-**13** in 20% yield with the pH substituent attached at C-4 of the ring. At 40 °C, however, a slightly better yield was attained (24%) (Table 3, entry 1). Note that this compound was earlier described in the literature [22].

In the case of *N*-Boc-protected cyclohexene β-amino ester (±)-**12**, the

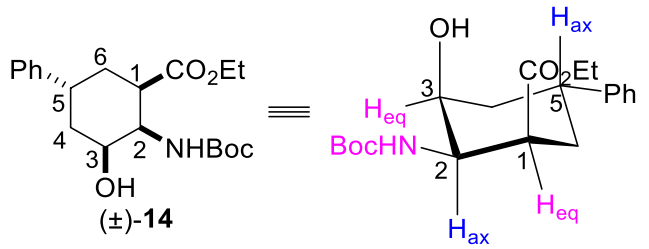


Fig. 7. Spatial orientation of axial and equatorial ring H-atoms in compound (±)-**14** (based on NMR studies).

reaction afforded selectively a single difunctionalized product (±)-**14**. The phenyl- and hydroxy-substituted product was isolated in a yield of 22% after 48 h by using CH_2Cl_2/MeOH (4:1) as the solvent system (protocol d) (Table 3, entry 2). The hydroxyl group formation in (±)-**14** could be a result of the aqueous workup of the reaction mixture. The structure of (±)-**14** has been elucidated by 2D NMR analysis indicating that the OH group is located at C-3 in a *cis* arrangement relative to the ester and carbamate moieties, while the pH group is connected to C-5, in a *trans* orientation in view of ester and carbamate (Fig. 7).

Next, our intention was to investigate and apply the above-mentioned conditions to cyclooctene-fused bicyclic lactam (±)-**15** studied earlier (Scheme 1b, ref [21a]). Thus, under the modified conditions, arylfluorinative transformation of lactam (±)-**15** afforded a mixture of five products instead of the expected four compounds. These are phenyl-substituted derivatives (±)-**16** and (±)-**17**, (the latter being a novel derivative not obtained earlier), phenylfluorinated isomers (±)-**18** and (±)-**19** obtained in 24% and 20% yields, respectively, and methoxy-substituted lactam (±)-**20**. When palladium acetate was employed instead of *bis*(acetonitrile)palladium dichloride (protocol b) [21a], the formation of the phenylfluorinated products proceeded with similar yields in the case of (±)-**18** (11%) and (±)-**19** (19%). The structure of compound (±)-**19** was also certified by X-ray diffraction analysis (Figure 8). Curiously, replacing MeOH with acetone in the solvent system (protocol c), the overall yield was not affected. However, the formation of (±)-**18** (24%) over (±)-**19** (9%) was significantly favored, resulting in a reversed ratio of roughly 2.7:1 (Scheme 3) The ratio of the formed isomers was determined based on the 1H NMR analysis of the crude mixture.

These results clearly indicate that both the palladium source and the solvent system exert a strong influence on the regioselectivity of the arylfluorinative difunctionalization process. Although the obtained products were isolated in modest yields, we consider their chromatographic separation a relative success.

3. Summary and outlook

In the current work our aim was to offer further insight into the Pd-catalyzed ring olefin bond arylfluorination of various functionalized cycloalkenes. We explored the scope and limitations of Pd-catalyzed arylfluorinative difunctionalization. Optimization of experimental conditions was accomplished on some *N*-protected cycloalkne beta-amino esters and cyclooctene-fused beta-lactam. During our studies commercial Pd-based catalysts and electrophilic fluorinating agents were

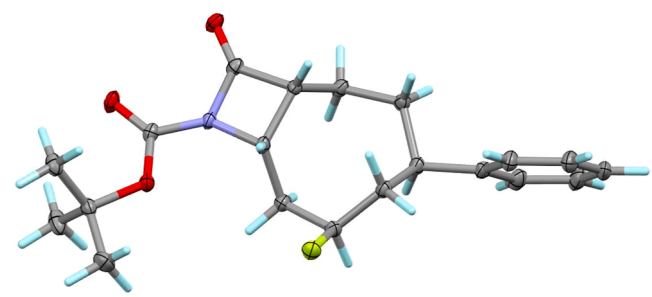
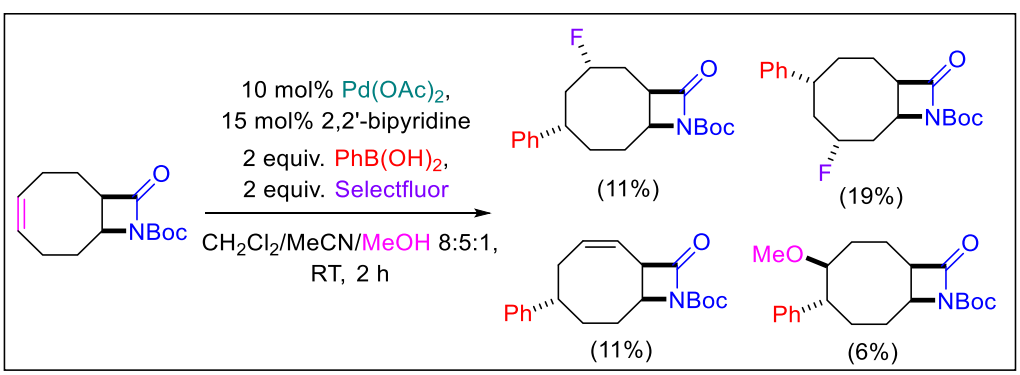
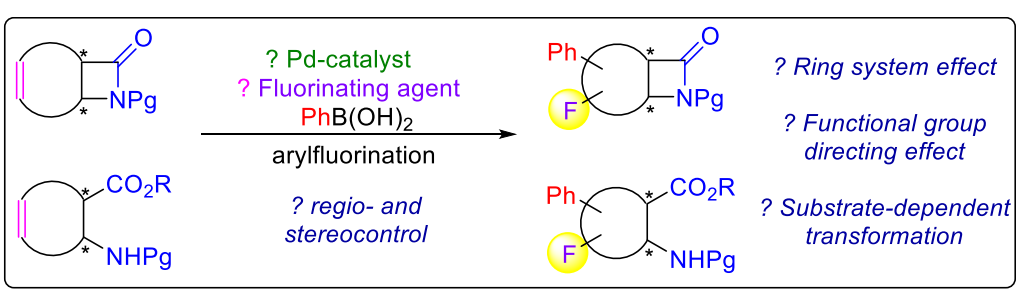


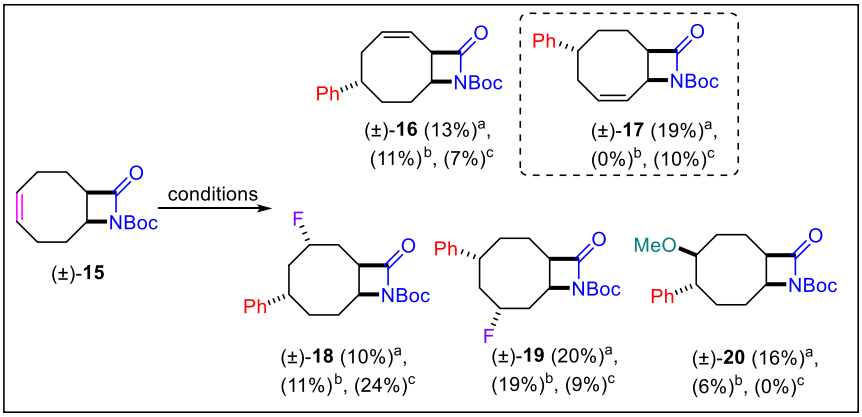
Fig. 8. Single crystal X-ray structure of fluorine-containing amino ester (±)-**19**. The ORTEP style representation was displayed at a 30% probability level for better clarity.



Scheme 1b. Earlier work: phenylfluorination of cyclooctene-fused β-lactam; overall yield: 47% [21a].



Scheme 2. Current goal: studies of fluorinating agents and Pd-catalyzed olefin arylfluorination of cycloalkene-based β-lactams and β-amino esters with diverse ring systems.



Scheme 3. Phenylfluorination of cyclooctene-fused β-lactam. [a]Conditions: $PdCl_2(CH_3CN)_2$ (10 mol%) in the presence of 2,2′-bipyridyl (15 mol%), $PhB(OH)_2$ (2 equiv), and Selectfluor (2 equiv) in CH_2Cl_2/MeCN/MeOH (8:5:1) at RT under Ar. [b]Using $Pd(OAc)_2$ (10 mol%) instead of $PdCl_2(CH_3CN)_2$ [21a]. [c]Using CH_2Cl_2/MeCN/acetone (8:5:1) instead of CH_2Cl_2/MeCN/MeOH (8:5:1).

investigated. Experimental conditions were also studied in view of ligand, solvent, temperature, additives, and reaction time. It should be concluded that, despite our efforts, the presented Pd-catalyzed transformations proceeded with modest yields. However, they gave interesting and relatively unpredictable products, considered utile building blocks in peptide chemistry. The structures of these compounds were elucidated not only by NMR spectroscopy but also by X-ray diffraction analysis. Cyclooctene-fused β-lactams and β-amino esters displayed distinct reactivity patterns, with the *cis* β-amino ester providing a single arylfluorinated product, while the *trans* analogue afforded only the phenyl-functionalized product. Notably, phenylfluorination of cyclooctene-fused azetidinone yielded two major fluorinated isomers whose ratios varied with the catalyst and solvent employed. These observations and experimental findings inspire us to perform further studies and investigations for the elucidation of the process and outcome of the reactions as well as on extensions of the arylfluorination regarding the Pd catalyst, the substitution pattern of substrate and arylating agent in view of the investigation of the arylboronic acid substituents, or functional group tolerance.

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Experimental procedure

First the catalyst solution was prepared by mixing 10 mol% palladium catalyst and 15 mol% ligand (2,2′-bipyridyl) in 3.0 ml CH_2Cl_2, and the resulting mixture was stirred under Ar atmosphere at room temperature for 15 min. The reactant solution was prepared by adding 0.5 mmol the starting compound to a mixture of 2 equiv $PhB(OH)_2$ and 2 equiv of fluorinating agent in 5 ml CH_2Cl_2, 5 ml MeCN, and 1 mL MeOH. Then the catalyst solution was added under Ar. The resulting reaction mixture was stirred at room temperature for the indicated time. Then, the reaction mixture was diluted with 25 ml CH_2Cl_2 and washed with 3 × 20 ml water (in the case of emulsion formation, some solid NaCl was added to the content of the separatory funnel). The organic phase was dried over Na_2SO_4. Finally, after filtering out the drying agent, the filtrate was evaporated under reduced pressure onto silica gel and purified by column chromatography (*n*-hexane-EtOAc).

Characterization of the newly synthesized substances and the spectra of the prepared compounds, 2D NMR analyses as well as X-.ray data are found in the Supplementary Material.

CRediT authorship contribution statement

Tamás T. Novák: Investigation, Formal analysis, Data curation. **Anas Semghouli:** Writing – original draft, Investigation, Formal analysis. **Tamás Holczbauer:** Investigation, Formal analysis. **Máté Sulyok-Eiler:** Investigation. **Pál T. Szabó:** Validation, Investigation. **Melinda Nonn:** Writing – original draft, Visualization, Investigation. **Gábor Turczel:** Supervision, Investigation, Data curation. **Santos Fustero:** Validation, Supervision. **Gábor Hornyánszky:** Supervision. **Jianlin Han:** Visualization, Validation, Investigation. **Loránd Kiss:** Writing – review & editing, Supervision.

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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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.molstruc.2026.146250.

Data availability

Data will be made available on request.

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