

Fluorinative Olefin Bond Functionalization of Selected Functionalized Cycloalkenes

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Abstract: Palladium-catalyzed ring olefin bond difunctionalization through arylfluorination of selected five-, six-, and seven-membered functionalized cycloalkenes has been studied. The arylfluorinative ring olefin bond difunctionalization was performed with phenylboronic acid, in the presence of Selectfluor and a palladium catalyst using azacyclic ligands in solvents.

Keywords: β -lactam · arylation · fluorination · palladium · substrate dependence

The arylfluorinations were found to be highly substrate and functional group dependent. Unfortunately, despite our efforts, reactions proceeded with modest yields. Surprisingly, however, they gave relatively unpredictable products. Possible mechanistic routes regarding the outcome of these interesting types of olefin bond difunctionalizations are also described.

1. Introduction and Aims

β -Lactams are structural motifs of high relevance in medicinal chemistry and pharmaceutical research, because of their wide range of biological properties, in particular, antibacterial activities. Major antibacterial agents contain the β -lactam element in various structural forms, such as heterocycle-fused (bicyclic) azetidin-2-ones (e.g., penicillins, cephalosporins) or functionalized azetidiones (monocyclic) (e.g., amino-substituted monobactams) (**Figure 1**).^[1–17] The azetidine-2-one moiety is the key element of the fluorine-containing blockbuster drug Ezetimibe, which is a popular non-statin cholesterol-lowering drug.^[18–21] Fluorine-containing β -lactams are intriguing structural elements, which might exhibit high pharmaceutical potential.^[13–15]

The high interest in biologically interesting β -lactams led to the design and preparation of various types of β -lactam-based antibiotics, thus giving rise to several synthetic procedures for the construction of the azetidin-2-one framework. Due to bacterial resistance towards various types of β -lactam derivatives, the synthesis of a novel generation of molecular entities with azetidin-2-one as structural motif constitutes a major challenge in synthetic chemistry. Importantly, apart from the construction of the azetidine-2-one system, in view of drug design, efforts on the construction of frameworks with a wide range of functionalities are highly desirable.

Therefore, the design and preparation of various highly functionalized β -lactam frameworks with biological potential generate a high interest in organic and pharmaceutical chemistry.

Organofluorine chemistry is considered to be an expanding field of organic and medicinal chemistry. Each year around 25%–30% of the newly introduced small-molecular-based drugs approved by FDA contain fluorine-containing active ingredients.^[18–21] Incorporation of a fluorine atom into the

structure of an organic molecule generates a profound effect on its acid–base character, lipophilicity, polar hydrophobicity, and metabolic stability, therefore increasing the bioavailability of a certain fluorine-containing compound with biological potential.^[18–33] Taking into account the above-mentioned importance of fluorine-containing molecular entities in drug research, it was desirable to develop synthetic methods for the incorporation of the fluorine atom in the structure of various bicyclic β -lactams.

Among fluorinative C–C double bond difunctionalizations, Pd-catalyzed arylfluorination is a relevant focus field, which

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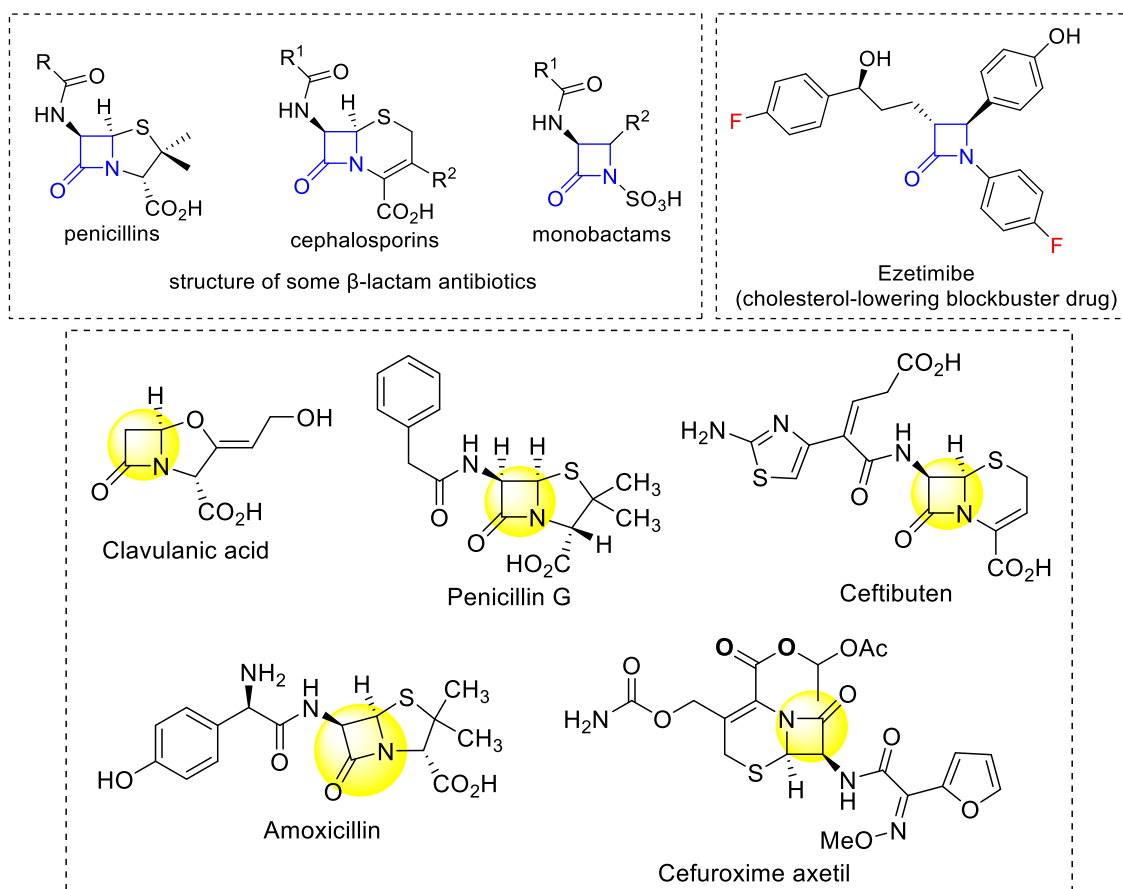


Figure 1. Some pharmaceutically relevant β -lactam-based products.

revealed increasing attention recently.^[34–39] Accordingly, our goal during this work was to create functionalized β -lactam motifs applying the procedure of our approach published earlier. This was based on the Pd-catalyzed phenylfluorinative difunctionalization of the ring C–C double bond of a cyclooctene-fused β -lactam (**Figure 2**).^[34,35]

We have decided to extend the above-depicted arylfluorination procedure in view of the application of novel cycloalkene-fused β -lactam starting compounds with the aim to study the effect of the architectural features of the substrate (e.g., ring size, location of the ring olefin bond, nature or presence of the *N*-protecting group) on the outcome of the transformation (**Figure 3**).

2. Results and Discussion

Racemic β -lactam (\pm)-**1** derived from 1,5-cyclooctadiene,^[40,41] the unprotected analog of the β -lactam studied earlier (Figure 2), was selected as the first model compound to be studied. Applying the reactions conditions utilized earlier, [Pd(OAc)₂, 2,2'-bipyridyl, phenylboronic acid, selectfluor, Figure 2], somewhat surprisingly, only traces of products could be observed with low conversion. Interestingly, by changing the nature of the

Pd catalyst, [from Pd(OAc)₂ to bis(acetonitrile)palladium dichloride] and testing several reaction conditions (solvent

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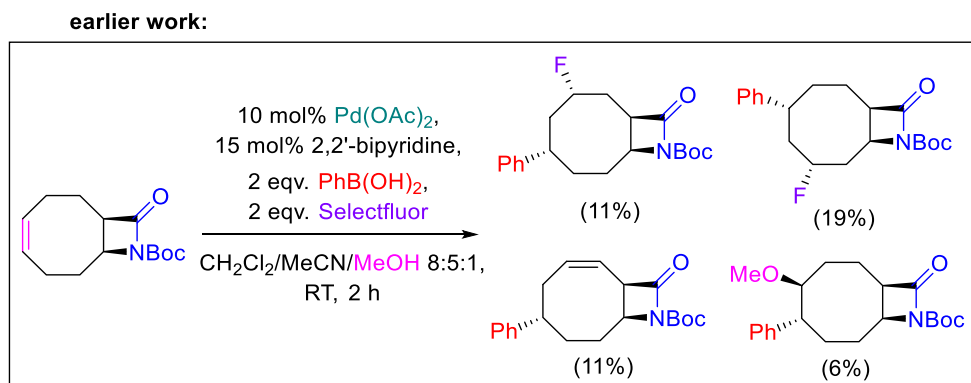


Figure 2. Earlier work: phenylfluorination of cyclooctene-fused β -lactam; overall yield: 47%.^[34]

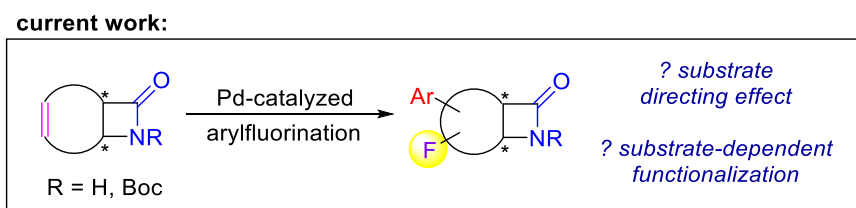


Figure 3. The aim of the current work: studies on the Pd-catalyzed fluorinative functionalization of some cyclooctene-fused β -lactam frameworks.

and ligand see Supporting Information), formation of a single product was observed. This was isolated and identified by 2D NMR analysis as phenylfluorinated compound (\pm)-**2**, containing the fluorine atom located at C-2, and the phenyl group on C-5 of the eight-membered ring (**Figure 4**). Formation of this product might be explained with the involvement of the Pd-promoted allylic-type migration, similar to that observed earlier.^[22–33] Although compound (\pm)-**2** could be isolated with a modest yield (25%), its exclusive formation during this transformation enabled an easy and rapid purification process. Note, that the *N*-Boc-protected analog of lactam (\pm)-**2** furnished four different compounds in a similar reaction (**Figure 2**). It should be noted that in a related reaction performed earlier with the Boc-protected counterpart, the fluorine atom was never attached to the C-2 atom of the cyclooctene ring. A mechanistic pathway for the formation of compound (\pm)-**2** is proposed and depicted on **Figure 2**, which involves, after transmetalation and olefin bond coordination step, a double allylic migration process as key steps followed by oxidative fluoronium transfer and reductive elimination (for similar transformation see also refs. 37, 38).

We have selected cyclooctene-fused β -lactams (\pm)-**3** and (\pm)-**4** derived from 1,3-cyclooctadiene as the next model compounds,^[40,42,43] which are regioisomers of the previously investigated derivatives (**Figure 2** and **4**). Contrary to the 1,5-cyclooctadiene-derived Boc-protected lactam (**Figure 2**), regioisomer (\pm)-**3** did not afford any identifiable product either in the presence of Pd(OAc)₂ or with (MeCN)₂PdCl₂. A different chemical behavior of (\pm)-**4** in comparison with its regioisomer (\pm)-**1** was observed. Under similar reaction conditions *N*-phenylation of (\pm)-**4** also took place, yielding compound

(\pm)-**5**, as the sole product, determined on the basis of the ¹H NMR data of the crude mixture. Unfortunately, only a low yield could be realized (**Figure 5**).

Our next goal was to extend the substrate scope by changing the skeletal architecture of the substrate. First, the 1,3-cyclohexadiene-derived protected and unprotected β -lactams ((\pm)-**6** and (\pm)-**7**)^[44] were studied. Again, it was noteworthy that the Boc-protected lactam (\pm)-**6** did not provide any isolable product, even though a series of experimental conditions were attempted. The outcome of the arylation/fluorination of the unprotected analog (\pm)-**7**, in turn, was more surprising. Contrary to the eight-membered scaffolds [(\pm)-**1** or (\pm)-**4** and compound (\pm)-**7**] under the same conditions furnished two products, which were separated by chromatography and isolated (31% overall yield). One of the products was identified as a phenyl-substituted cyclohexene-fused β -lactam (\pm)-**9** with the Ph group connected at C-5, while the olefin bond located between C-3 and C-4 of the six-membered ring. The structure of the other product, ((\pm)-**8**) was elucidated by NMR and X-Ray analyses. To our surprise, it was found to be a compound resulting via the opening of the azetidinone ring and the Ph substituent located at C-1 (**Figure 6** and **7**).

Although the structure of (\pm)-**8** at the first evaluation was somehow surprising for us, the possible mechanistic route towards its formation is proposed and can be interpreted as depicted on **Figure 8**. Note that this suggested pathway is not yet supported by molecular modeling or computational studies. Further detailed investigations, based on theoretical chemical calculations are needed in order to elucidate the exact process.

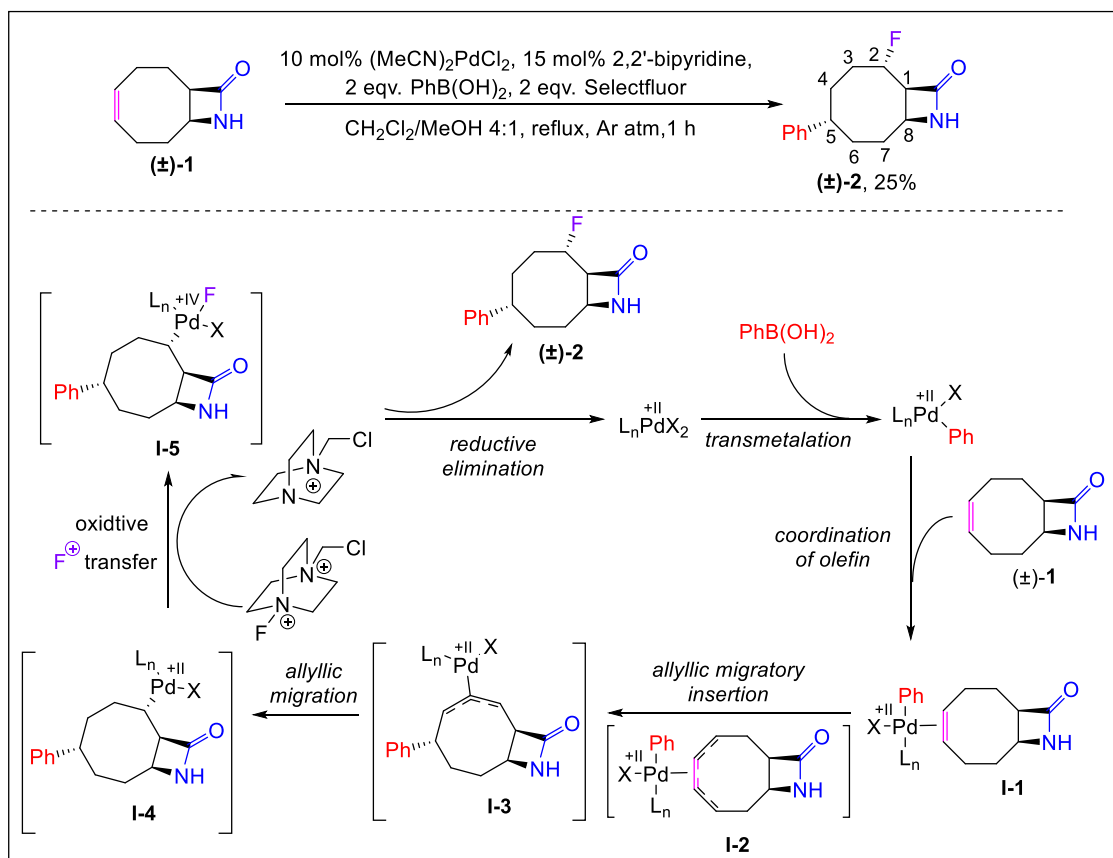


Figure 4. Pd-catalyzed olefin bond functionalization of 1,5-cyclooctadiene derived unprotected cyclooctene-fused β -lactam.

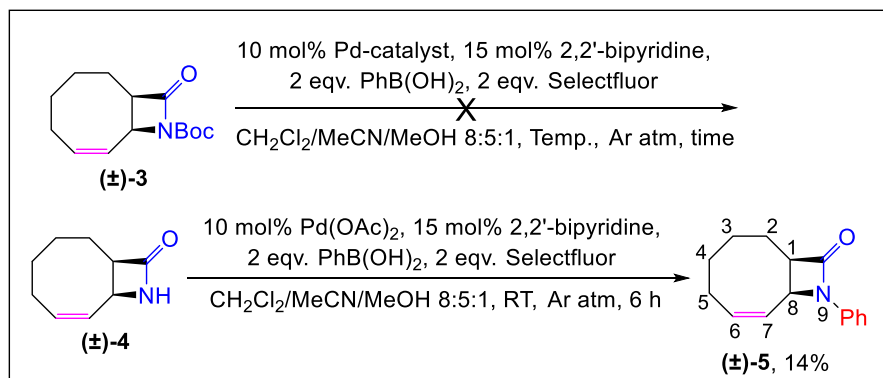


Figure 5. Pd-catalyzed olefin bond functionalization of unprotected and Boc-protected cyclooctene-fused β -lactam derived from 1,3-cyclooctadiene.

After the transmetalation between Pd and phenylboronic acid, coordination to the C–C double bond may occur as a result of a possible tautomerization in lactam **(±)-6** (through **A**) by forming structure **B**. Then a new C–C bond is formed through Ph transfer, and the Ph group is attached onto C-1 forming structure **C** across a backside attack. Attack, through a nucleophilic addition step (A_N) of MeOH as solvent to the amide sp^2 C atom

(which is apart of a strained β -lactam framework), followed by carbonyl bond reformation with simultaneous C–C breaking involving an $\text{S}_{\text{N}}\text{Ac}$ -like process across **D** and **E**, followed by proton transfer give structure **(±)-8** (Figure 8). It should be mentioned that this proposed route is not yet supported by computational studies. This mechanistic pathway proposal has been depicted taking into consideration the elucidated structure of

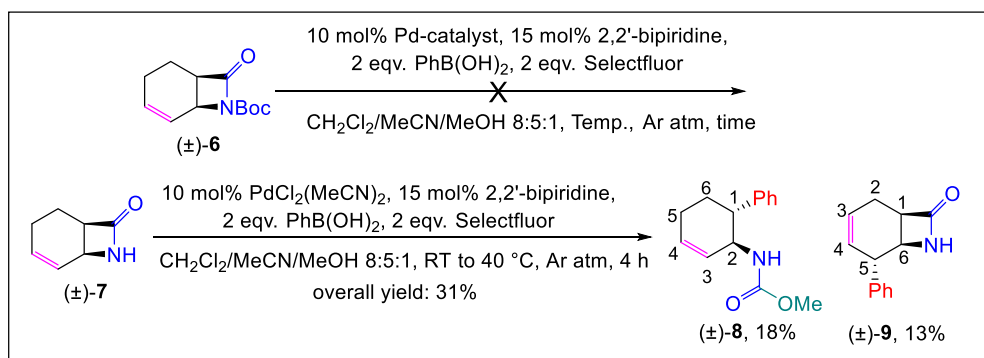


Figure 6. Pd-catalyzed olefin bond functionalization of 1,3-cyclohexadiene-derived, unprotected and Boc-protected cyclohexene-fused β -lactam.

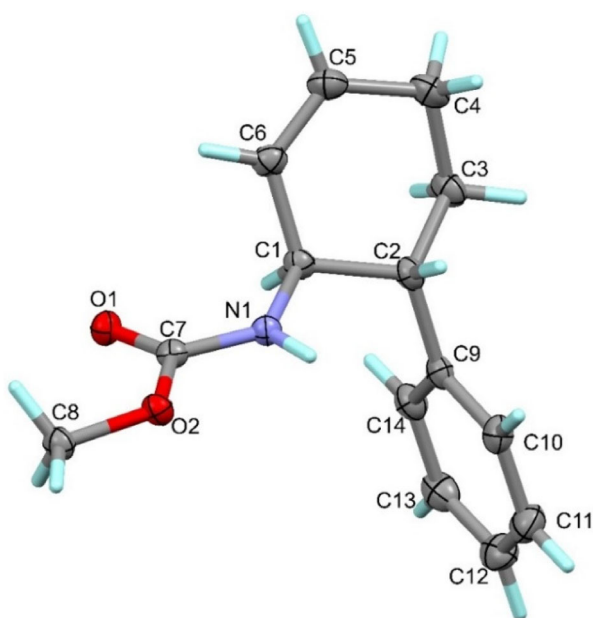


Figure 7. Single-crystal X-Ray structure of compound (\pm)-8.

the formed product (\pm)-8, in order to provide a plausible explanation for its formation.

The somewhat unpredictable outcome of the arylfluorination reactions of bicyclic β -lactams was also observed in the case of the 1,4-cyclohexadiene-derived cyclohexadiene-fused azetidinone isomers (\pm)-10 and (\pm)-11.^[45,46] During the arylfluorination of Boc-protected lactam (\pm)-10 a single product could be isolated. Its structure was confirmed by NMR analysis as to be (\pm)-12, with the phenyl group connected at C-4 and the olefin bond located between C-2–C-3 of the six-membered ring (Figure 9).

When unprotected lactam (\pm)-11 was subjected to phenylfluorination under similar conditions, it provided two products in 32% overall yield. After chromatographic separation and structure elucidation by NMR spectroscopy, the minor derivative was identified as phenylfluorinated compound (\pm)-14 with the Ph

group bonded to C-3 and fluorine at C-5 of the cyclohexane ring, both possessing *cis* relative steric arrangement (Figure 9). The major product of this reaction was identified to be phenylated compound (\pm)-13, whose formation might be explained analogously to that of (\pm)-8.

Again, the behavior of the cyclopentadiene-derived protected or unprotected cyclopentene-fused lactams (\pm)-15 and (\pm)-16 was curious.^[47,48] While unprotected compound (\pm)-16 did not afford any identifiable product, its Boc-protected counterpart resulted in phenylated compound (\pm)-17 as the sole product in a selective manner (Figure 10).

It should be noted that according to our actual knowledge, there is no plausible explanation for the interesting but rather rhapsodic behavior of the above-studied cycloalkene-fused β -lactams (Figure 4–10). Consequently, further systematic investigations and optimizations with the aid of computational studies should be performed for better interpretation and elucidation of these intriguing transformations.

Finally, our idea was to extend the substrate scope and to carry out the above-presented Pd-catalyzed arylfluorination with some representative structural elements: a substituted cyclopentene (18), a substituted cyclohexene (19), an aromatic ring-fused cyclopentene (indene, 20), and a functionalized cyclic diene (21) (Table 1). The reactions were performed under various experimental conditions, and we found that under these conditions Pd(OAc)₂ proved to be superior to PdCl₂(CH₃CN)₂. Benzyl ester 18 with a cyclopentene ring under phenylfluorination afforded three products in 35% overall yield. These could be separated and isolated by means of chromatography, their structure being determined based on 2D NMR data. Two compounds [(\pm)-22 and (\pm)-23] have been identified as regioisomers of phenyl-substituted elimination products, while the third compound ((\pm)-24) was identified as an arylfluorinated scaffolds with the Ph and fluorine possessing a *trans* relative steric position. Cyclohexene diester 19 when underwent Pd-catalyzed arylation also gave two products in 1:1 ratio in 40% overall yield, which could also be separated and isolated. Based on NMR analysis, one of the compounds was elucidated to be phenylated compound 25. The other, besides the Ph ring, possessed a hydroxyl group

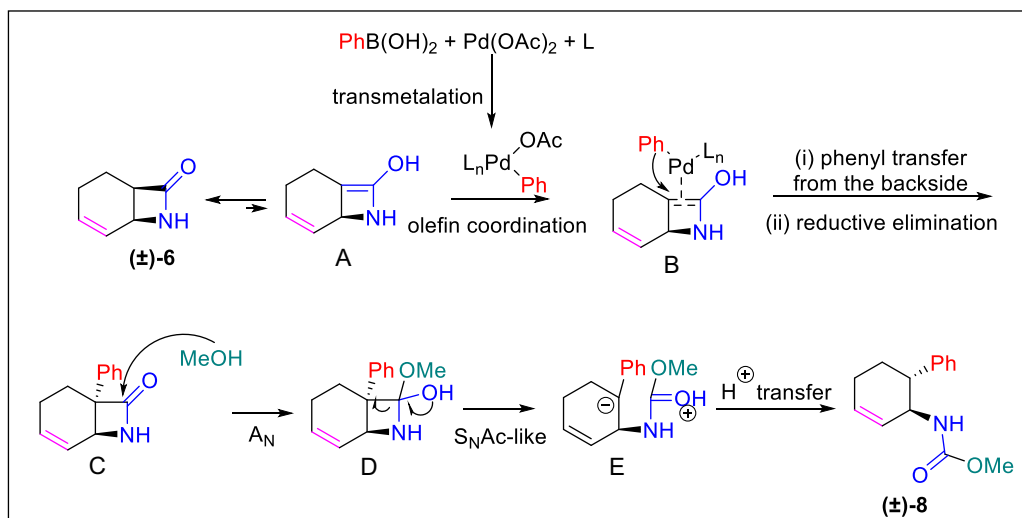


Figure 8. A suggested mechanistic route for the formation of compound (±)-8.

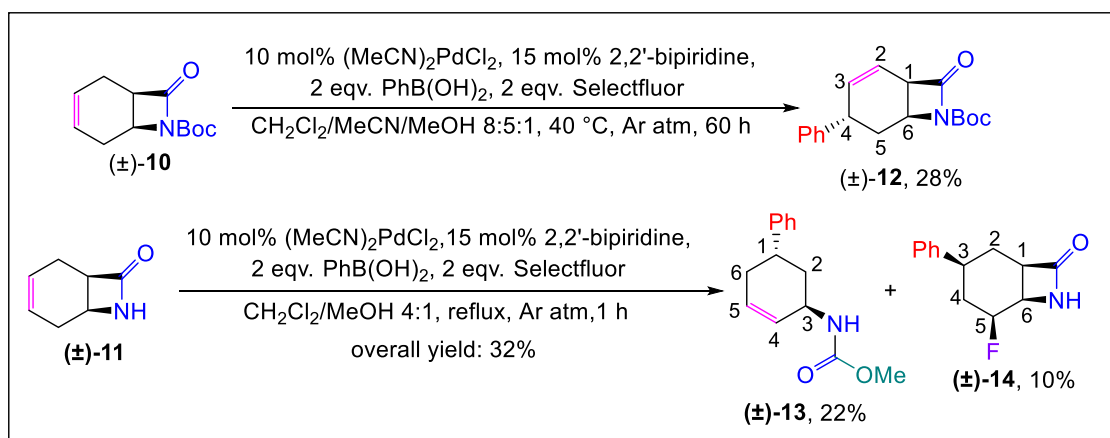


Figure 9. Pd-catalyzed olefin bond functionalization of unprotected and Boc-protected cyclohexene-fused β -lactams derived from 1,4-cyclohexadiene.

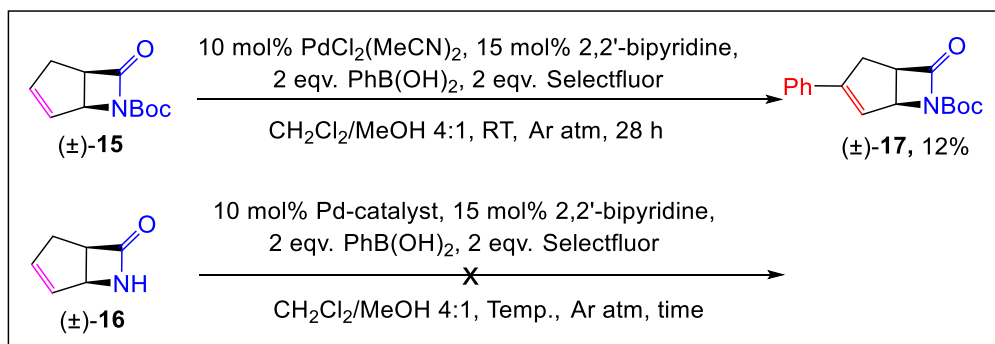
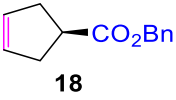
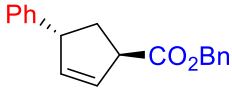
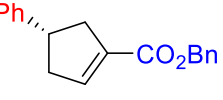
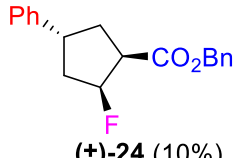
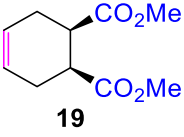
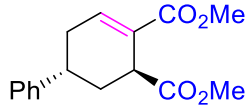
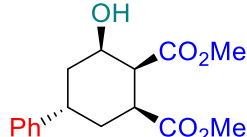
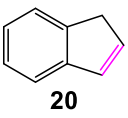
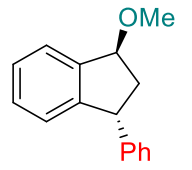
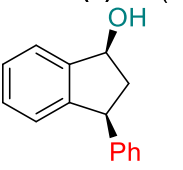
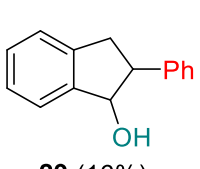
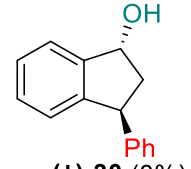
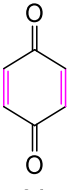
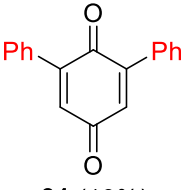


Figure 10. Pd-catalyzed olefin bond functionalization of unprotected and Boc-protected cyclopentene-fused β -lactams derived from cyclopentadiene.

Table 1. Fluorinative difunctionalization of some functionalized cycloalkene scaffolds.

Substrate	Products	Time	Yield
 18	 (±)-22 (13%)	2 h	22: 0% ^{a)} , 13% ^{c)} 23: 3% ^{a)} , 12% ^{c)} 24: 0% ^{a)} , 10% ^{c)} overall yield: 35%
 (±)-23 (12%)			
	 (±)-24 (10%)		
 19	 (±)-25 (20%)	23 h	25: 0% ^{a)} , 20% ^{c)} 26: 0% ^{a)} , 20% ^{c)} overall yield: 40%
	 (±)-26 (20%)		
 20	 (±)-27 (12%)	4 h	27: 5% ^{a)} , 12% ^{c)} 28: 0% ^{a)} , 6% ^{c)} 29: 0% ^{a)} , 16% ^{c)} 30: 2% ^{a)} , 8% ^{c)} overall yield: 42%
	 (±)-28 (6%)		
	 29 (16%)		
	 (±)-30 (8%)		
 21	 31 (19%)	21 h	0% ^{a)} , 19% ^{b)}

^{a)}Reaction conditions: Standard conditions: PdCl₂(CH₃CN)₂ (10 mol%) in the presence of 2,2'-bipyridyl (15 mol%), PhB(OH)₂ (2 eqv.), and Selectfluor (2 eqv.) in CH₂Cl₂/MeCN/MeOH (8:5:1) at room temperature under argon. ^{b)}Same as (a) except temperature 40 °C was used. ^{c)}Same as (a) except using Pd(OAc)₂ (10 mol%) instead of PdCl₂(CH₃CN)₂.

(most eloquent after aqueous workup). The indene C–C double bond in **20** could also be difunctionalized, giving four separable products in a 42% overall yield. Three of these products were isomers of phenyl- and hydroxy-substituted derivatives [*cis* (±)-**28**, *trans* (±)-**30**, and regioisomer **29**] and methoxy-substituted compound (±)-**27**. Unfortunately, the stereochemical structure, the relative arrangement of the Ph and OH groups in **29** could not be determined. Finally, arylfluorination of *p*-benzoquinone gave diphenylated product **31** as a single product (Table 1). This compound was earlier reported in the literature.^[49]

3. Summary and Outlook

In this work we investigated the Pd-catalyzed arylfluorination of the olefin bond in various cycloalkene-fused β-lactams. Substrate characteristics, e.g., ring size, location of the ring C–C double bond, as well as the nature of the *N*-protecting group were found to have a high influence on the outcome of the fluorinated difunctionalization of the olefin bond. Phenylfluorination was attempted with some selected functionalized cycloalkenes (substituted cyclopentene, substituted cyclohexenes, annulated cyclopentene), which resulted in various phenylated or fluorinated

scaffolds. It should be noted that these Pd-catalyzed transformations—despite our all efforts—unfortunately proceeded with modest yields. Nevertheless, interesting and relatively unpredictable products were formed. The experimental findings inspire us to perform further studies and investigations for the optimization of reaction conditions, the elucidation of the reaction pathways, as well as exploring further extensions of the arylfluorinative transformations regarding the Pd catalyst, the substitution pattern of substrate, and the arylating agent.

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Conflict of Interest

The authors declare no conflict of interest.

Author Contributions

Tamás T. Novák: investigations. **Melinda Nonn:** investigations. **Gábor Turczel:** formal analysis. **Pál T. Szabó:** formal analysis. **Máté Sulyok-Eiler:** formal analysis. **Tamás Holczbauer:** formal analysis. **Anas Semghouli:** data curation. **Santos Fustero:** validation, conceptualization. **Loránd Kiss:** conceptualization and writing. **Jianlin Han:** supervision and validation. **Gábor Hornyánszky:** supervision and validation.

Data Availability Statement

The generated data during this research are included and can be found in the Supporting Information of this paper. All data generated or analyzed during this study are included in this published article [and its Supporting Information files].

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