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# A Convenient Synthesis of Some Phenyl-Substituted Aliyclic β-Amino Esters and β-Lactams

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A convenient synthetic procedure has been developed for the access of phenyl-substituted alicyclic β-amino acid derivatives. The substrate-directed palladium-catalyzed cross-coupling of phenylboronic acid with five- or six-membered cycloalkene β-amino esters and bicyclic β-lactams in the presence of Selectfluor as oxidant provided phenyl-substituted alicyclic β-amino esters and azetidin-2-ones. Phenylations were investigated under various experimental conditions with different ligands and solvent systems. The structural architecture of the starting compounds and the position of their ring olefin bond influenced and predetermined the structure of the products.

## Introduction

Alicyclic β-amino acids are interesting molecular elements in medicinal chemistry, being components of natural products, bioactive compounds as well as precursors of various β-lactam scaffolds. Some representative small-molecular entities of this class of compounds are known as antifungal or antibacterial agents. The natural *Cispentacin* (**1**) and the synthetic *Icofungipen* (**2**) and *BAY Y9379* (**3**) are probably the most important scaffolds in this area. Natural representatives, the four-membered *O*-heterocyclic amino acid *Oxetin* (**4**) and the hydroxylated six-membered derivative *Oryzoxymicin* (**5**) exhibit antibiotic activities. It is well known, that the conformationally constrained alicyclic β-amino acids (e.g. *Transpentacin*, **6**) may function as building blocks for the construction of novel antimicrobial peptides, which might have interest in pharmaceutical research. Furthermore, *Tilidine* (**7**) the phenyl-substituted cyclohexene β-amino ester representative is a commercial analgesic drug (Figure 1).[1]

Alicyclic β-amino acid moieties are parts of various bioactive products such as nucleoside antibiotics (e.g. *Amypurimycine*, **8**), antitumoral agents (e.g. *CEP-28122*, **9**), and antiviral products (e.g. *Pimodivir*, **10**) (Figure 1).[1]

Many functionalized alicyclic β-amino acid derivatives possessing various functional groups or atoms (hydroxy, amino, azido, triazole, isoxazoline, alkyl, alkenyl, fluoro, difluoro, etc.) attached onto their carbocyclic skeleton were synthesized and described in the literature;[1a,b,2] however, only relatively few aryl-substituted representatives are known in the literature so far.[3] Moreover, the methods affording access to arylated alicyclic β-amino acid derivatives suffer from some limitations, such as applicability, generalization or extendibility.[3]

Conformationally rigid alicyclic β-amino acids are interesting building elements for the synthesis of novel type of oligopeptides with important pharmacological potential. Consequently, they have significant relevance in drug design.[4] The aromatic–aromatic (π–π) and CH–π interactions in and between various helix-type structures might have significant influence on the secondary or tertiary arrangements of oligopeptides.[5–7] Therefore, amino acids with an aryl unit in their structure have received high significance in peptide research. Although a number of aromatic, non-usual, open-chain or cyclic α-amino acids were synthesized and are known to have medicinal use, acyclic β-amino acid analogs are much less abundant,[6] while the number of cyclic β-amino acids with an aromatic framework is even more limited.

### Aims

Considering the high importance of conformationally restricted, arylated amino acids and that of the analgesic drug *Tilidine* (**7**) (Figure 1, a phenyl-substituted cyclohexene β-amino acid derivative), our aim focused on the development and extension of a regio- or stereoselective synthetic approach to the synthesis of phenyl-substituted alicyclic β-amino acid derivatives (with the phenyl group connected either to an $sp^3$ or olefin carbon atom). These compounds with a unique architecture incorporating planar and three-dimensional elements in their structure,[8] might be highly useful in peptide-based drug research as well as in small-molecular-based drug design.

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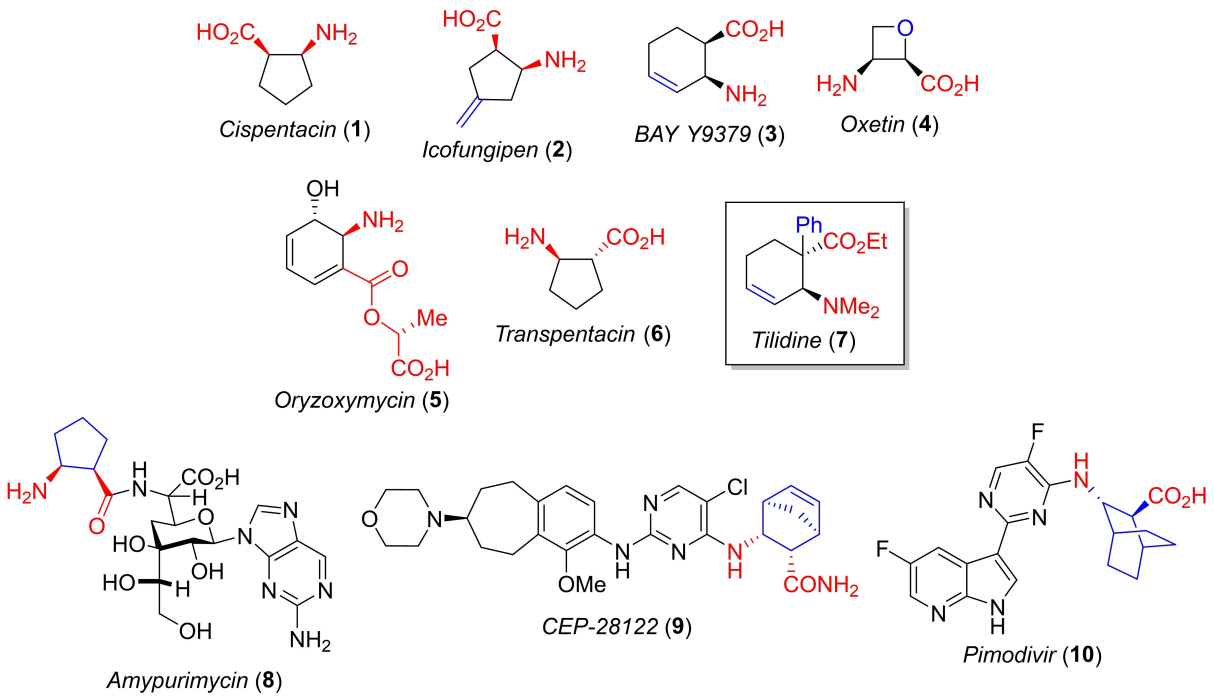



**Figure 1.** Some alicyclic β-amino acid derivatives and with biological relevance and some bioactive products with an alicyclic β-amino acid moiety.

## Results and Discussion

In our current short report, we describe a convenient, improved, and extended methodology to the access of various phenyl-substituted cyclic β-amino esters and bicyclic β-lactams. For this purpose, as starting model compounds, we selected some representative racemic cyclohexene-based β-amino ester isomers ((±)-**11**–(±)-**13**), differently protected β-amino esters with a cyclopentene skeleton ((±)-**14**–(±)-**16**), as well as bicyclic β-lactam derivative (±)-**17** (Figure 2).

Our first experiments started with the transformation of racemic ethyl (1R*,2S*)-2-((*tert*-butoxycarbonyl)amino)cyclohex-3-ene-1-carboxylate ((±)-**11**) under oxidative boron Heck type reaction conditions. In a systematic investigation, amino ester (±)-**11** was reacted with $PhB(OH)_2$ as the aryl source (note: the structure of Tilidine contains a phenyl group), $Pd(OAc)_2$ as catalyst, and Selectfluor as oxidant in the presence of 2,2′-bipyridyl or 4,4′-di-*tert*-butyl-2,2′-bipyridyl as ligand sources in various solvent systems. Since the starting amino ester is soluble in organic solvents, while Selectfluor is soluble only in highly polar solvents, we performed the transformation in different bi- or triphasic solvent systems such as $CH_2Cl_2/H_2O$/MeCN (38%), $CH_2Cl_2$/MeCN (39%), THF/$H_2O$ (29%), $CH_2Cl_2/H_2O$/THF (31%). The reaction provided selectively a single arylated amino ester product with the highest yield attained in $CH_2Cl_2$/MeOH and in the presence of 2,2′-bipyridyl (isolated yield 71%, Scheme 1). In comparison, in the presence of 4,4′-di-*tert*-butyl-2,2′-bipyridyl ligand, under similar experimental conditions, the yield was 54%. It should be noted, that according to literature data, under similar experimental conditions (phenylboronic acid, palladium acetate, Selectfluor, 4,4′-di-*tert*-butyl-2,2′-bipyridine, and a triphasic solvent system $CH_2Cl_2/H_2O$/MeCN), aryl-fluorination of the olefin bond of unsaturated sulfonamides

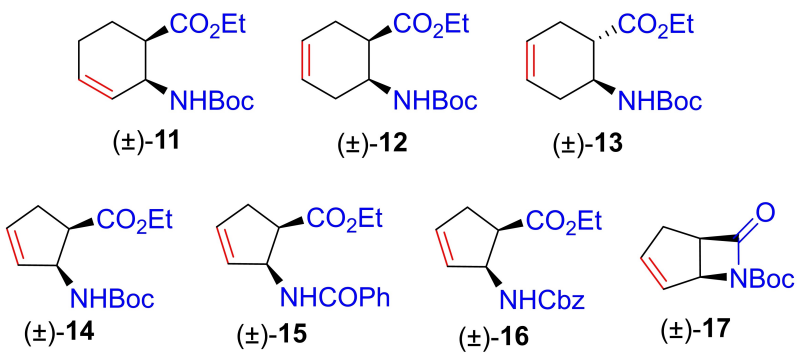
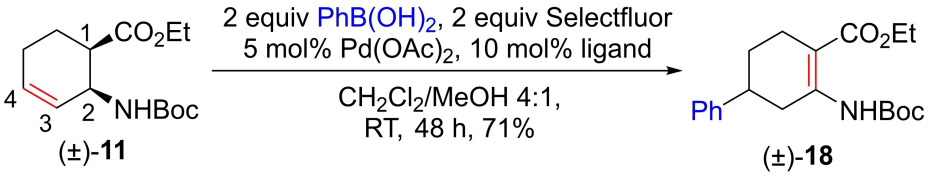



**Figure 2.** Starting model compounds used in the current work.




**Scheme 1.** Phenylation of cyclohexene β-amino ester (±)-**11** (ligand: 2,2′-bipyridyl: yield 71% or 4,4′-di-*tert*-butyl-2,2′-bipyridyl: yield 54%).

took place because of the directing effect of the sulfonyl group.[9]

In the case of phenylation of amino ester (±)-**11** a substrate-directing effect was also observed. According to 2D NMR analysis, product (±)-**18** was obtained in a regioselective manner with the phenyl group located on C-4 of the cyclohexene ring. In addition, the olefin bond was located between C1 and C2 as a result of the migration of double bond (Scheme 1).

The outcome of this reaction may be explained by an oxidative boron Heck reaction followed by olefin bond migration driven by the extension of conjugation in formed product (±)-**18**. This compound was obtained earlier under common Heck arylation conditions.[3a] Oxidative Heck reactions were reported as side reactions of arylfluorinations (for their general mechanism, see Figure 3).[10] Thus, after transmetallation and coordination to the olefin bond, 1,2-carbopalladation takes place. Next, β-hydride elimination might furnish two regioisomeric products with arylated olefinic moieties in their structures. Finally, oxidation of the $Pd^0$ species regenerates the $Pd^{2+}$ type catalyst.

The substrate-directing short pathway for the formation of phenylated β-amino ester (±)-**18** is depicted in Scheme 2. Due to the coordinating ability of the carbamate *O*-atom to palladium, the olefin coordination and carbopalladation steps proceeded in a regioselective manner with the attachment of the phenyl group at C-4, while Pd is located at C-3, closer to the NHBoc group, thus forming a six-membered chelate ring (**T1**). Next, β-elimination, followed by active H deprotonation/olefin bond migration/reprotonation steps (**T2**/**T3**/**T4**) result in final product (±)-**18** (Scheme 2).

In continuation, ethyl (1R*,2S*)-2-((*tert*-butoxycarbonyl)amino)cyclohex-4-ene-1-carboxylate ((±)-**12**), a regioisomer of (±)-**11** was submitted to phenylation under similar experimental conditions. In this case a phenyl-substituted product was isolated in 69% yield, whose structure was identified by means of 2D NMR and MS data. In product (±)-**19**, the phenyl group is attached at C-4, while the C=C double bond is located between C-4 and C-5 of the six-membered ring (Scheme 3).

Similar to (±)-**11**, in the regioselective phenylation of (±)-**12**, the carbopalladation step most probably takes place with the involvement of a more stable six-membered chelate ring intermediate (**T5**), in which Pd is attached at C-5. Note that a chelation between Pd and the carbamate *O*-atom would generate a less stable seven-membered ring intermediate. Next, due to extended conjugation, β-elimination afforded phenylated product (±)-**19** (Scheme 4).

Our next aim was to study phenylation of (1S*,2S*)-2-((*tert*-butoxycarbonyl)amino)cyclohex-4-ene-1-carboxylate ((±)-**13**),

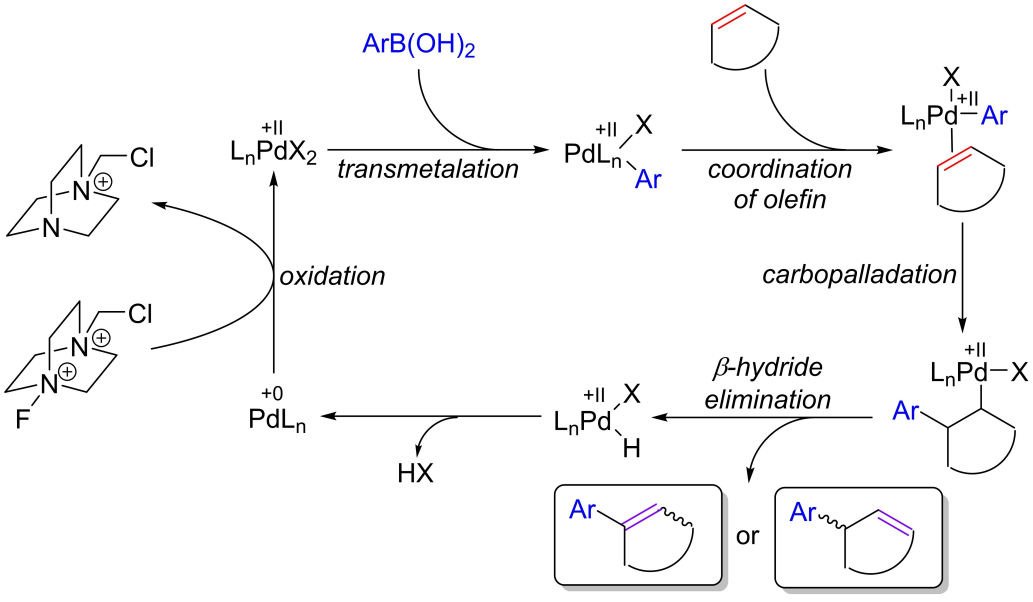
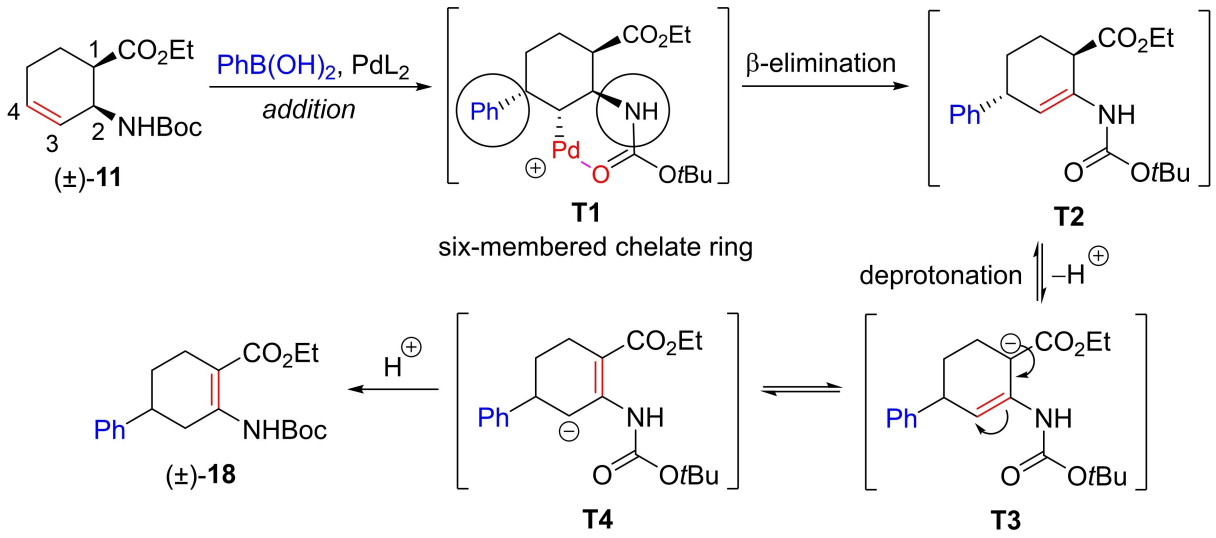
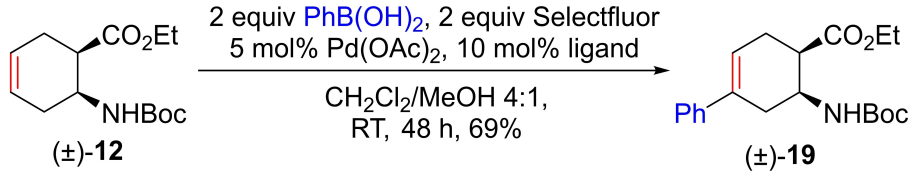


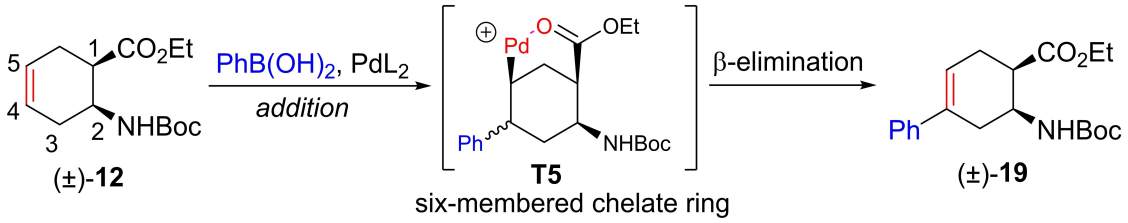

**Figure 3.** Proposed pathway for cycloalkene arylation.




**Scheme 2.** Formation of phenyl-substituted β-amino ester (±)-**18**.



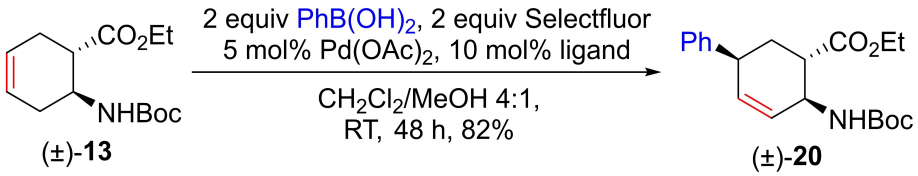

**Scheme 3.** Phenylation of cyclohexene β-amino ester (±)-**12** (ligand: 2,2′-bipyridyl).




**Scheme 4.** Formation of phenyl-substituted β-amino ester (±)-**19**.

the *trans* stereoisomer of its *cis* counterpart (±)-**12**. Under similar experimental conditions, amino ester (±)-**13** underwent regio- and stereoselective phenylation, most probably due to steric factors: the aryl group attacked the ring olefin bond from the opposite side related to the ester group.[3a,11] Thus, contrary to (±)-**12**, it furnished a product ((±)-**20**) with the aromatic group connected to C-5 and the olefin bond located between C3 and C4 of the six-membered ring. Its structure and stereochemistry were certified by means of COSY, HSQC HMBC, and NOESY experiments as well as MS data (Scheme 5, Figure 4).

Turning to the investigation of smaller ring systems and the nature of the amino protecting group, Boc/COPh/Cbz-protected cyclopentene *cis* amino esters (±)-**14**, (±)-**15**, and (±)-**16** were subjected to phenylation reaction. It was observed that the ring size had no effect on the outcome of the reaction. These cyclopentene-based compounds show certain similarity to six-membered amino ester (±)-**11** with an allyl-amine element in




**Scheme 5.** Phenylation of cyclohexene β-amino ester (±)-**13** (ligand: 2,2′-bipyridyl).

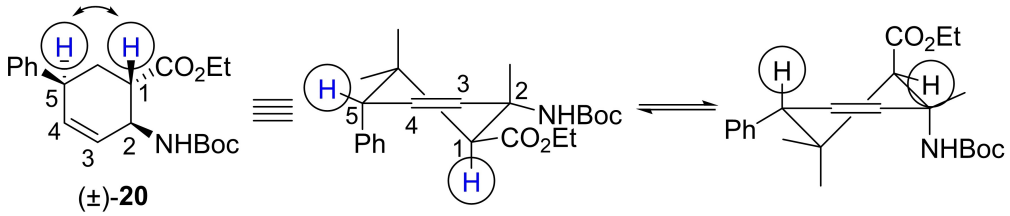
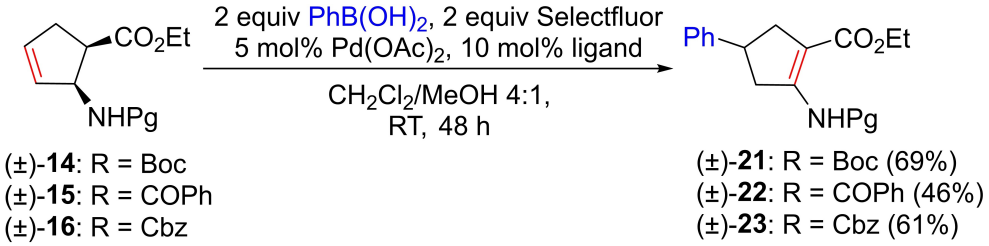
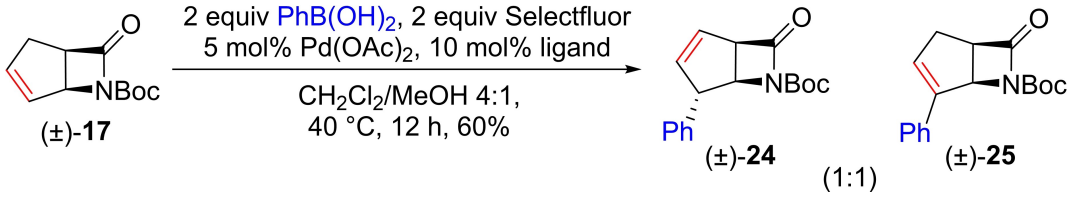



**Figure 4.** Conformational structures of compound (±)-**20**.




**Scheme 6.** Phenylation of cyclopentene β-amino esters (±)-**14**, (±)-**15**, and (±)-**16** (ligand: 2,2′-bipyridyl).




**Scheme 7.** Phenylation of cyclopentene-fused β-lactam (±)-**17** (ligand: 2,2′-bipyridyl).

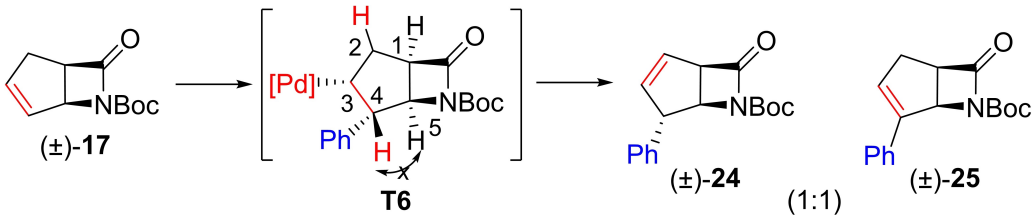



**Figure 5.** Formation of phenylated products (±)-**24** and (±)-**25**.

their structure. Accordingly, the oxidative boron Heck type reaction of (±)-**14**, (±)-**15**, and (±)-**16** proceeded similarly to (±)-**11**, in a regioselective manner, giving across olefin bond migration the corresponding phenylated products (±)-**21**, (±)-**22** and (±)-**23** (Scheme 6). Note that these derivatives were also synthesized earlier according to the traditional Heck reaction.[3a]

Our next goal was to investigate the behavior of a model compound with a slightly lower ring strain under similar oxidative Heck conditions. For this purpose, we selected unsaturated bicyclic β-lactam (±)-**17** by investigating various conditions in view of solvent and ligand. Interestingly, this transformation, performed under similar conditions used in the reactions described above, proved to be non-selective. Namely, phenyl-substituted products (±)-**24** and (±)-**25** were formed in approximately 1:1 ratio. They could be separated by means of column chromatography, isolated in moderate yields and their structures were elucidated with COSY, HSQC HMBC, and NOESY analyses and MS data (Scheme 7), the pathway to these products being illustrated on Figure 5. The NOESY data unequivocally indicates the trans relative orientation of the H atoms from position 4 and 5 in compound (±)-**24**, no NOESY interaction between these protons was observed.

## Conclusions

In the current work a preliminary insight into an improved method for the synthesis of some phenyl-substituted alicyclic amino esters has been given. The Pd-catalyzed substrate-dependent phenylation procedure with boronic acid used some representative β-amino esters with a cyclohexene or cyclopentene framework as starting model compounds. This method was slightly superior in yields compared with the traditional

Heck methodology (Pd catalyst, phosphane ligand and aryl-halide). The method could be applied in the phenylation of a cyclopentene-fused β-lactam as well. Further extensions of the reported method in view of the application of novel substrate model compounds as well as of other phenylating sources are currently being investigated in our laboratory.

## Experimental

### General Methods

All commercial reagents and solvents were used as received from the suppliers, without further purifications. $^{1}H$ NMR and $^{13}C$ NMR spectra were recorded at 300 MHz using $CDCl_3$ as solvent. Chemical shifts are given in ppm relative to TMS for $CDCl_3$. HRMS measurements were performed using a Waters QTOF Premier high resolution mass spectrometer (Waters, Manchester) using positive electrospray mode.

### General procedure for the phenylation reaction

A catalyst solution was prepared by mixing 5 mol% $Pd(OAc)_2$ (12 mg) and 10 mol% ligand (2,2′-bipyridyl or 4,4′-di-*tert*-butyl-2,2′-bipyridyl) in 2.0 ml $CH_2Cl_2$, and the resulting mixture was stirred at room temperature for 20 min. The reactant solution was prepared by adding 6 ml $CH_2Cl_2$ and 2 ml MeOH to the mixture of 0.5 mmol starting compound, 2 equiv $PhB(OH)_2$, and 2 equiv Selectfluor. Argon gas was bubbled through the reactant solution at room temperature for 10 minutes then the catalyst solution was added to this mixture. The resulting reaction mixture was stirred at the temperature and time indicated (monitored by TLC). Then, the reaction mixture was diluted with 25 ml $CH_2Cl_2$ and washed with 3×20 ml brine. The organic phase was dried over $Na_2SO_4$. Then the drying agent was filtered out, the resulting filtrate was evaporated on silica gel and purified by column chromatography.

## Supporting Information Summary

Characterization data, and NMR and MS spectra of the synthesized compounds are found in the Supporting Information.

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## Conflict of Interests

The authors declare no conflict of interest.

## Data Availability Statement

Research data are not shared.

**Keywords:** amino acids · phenylation · cycloalkenes · olefin functionalization · palladium catalysis

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