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Pd-catalyzed carbonylative α-arylation of azlactones: A formal four-component coupling route to α,α-disubstituted amino acids ☆

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ABSTRACT

We report on a Pd-catalyzed carbonylative α-arylation of azlactones derived from alanine, providing facile access to α,α-disubstituted amino acids after an alcoholysis step. A range of aryl iodides proved to be suitable substrates in this formal four-component approach, providing the desired products in good to high yields. Other amino acids, such as methionine, leucine and phenylalanine could be functionalized in a similar manner with this methodology. The possibility for isotope labeling (^{13}C, ^{2}H) was demonstrated, as well as chemoselective transformations of the tricarbonyl-containing molecules.

5-Oxazolinones, also known as azlactones, represent an important class of masked amino acids, which are susceptible to a wide array of chemical transformations [1–3]. Amino acids can easily be converted into this cyclic compound by a simple two-step protocol involving *N*-benzoylation followed by ring closure with DCC or other coupling reagents (Scheme 1a). 5-Oxazolinones display two electrophilic sites (positions 2 and 5) and a pro-nucleophilic site at position 4. Given the resonance structures of the corresponding enolate of 5-oxazolinones, a partial negative charge can be located at the 2-position, providing some nucleophilicity at this carbon as well (Scheme 1b). Consequently, much of the reported chemistry dealing with azlactones focuses on either nucleophilic ring-opening of the lactone or reactions of electrophiles at the oxygen of position 5 or on the remaining two ring carbon centers (positions 2 and 4) [1]. Examples of transformations involving the α-carbon include alkylation [4,5], allylation [6,7], aldol-[8], Michael-[9–13] and Mannich reactions [14–16]. Acylation of the α-carbon (position 4) is also possible; however, this requires initial *O*-acylation of the enolate followed by a Steglich rearrangement (Scheme 1c) [17]. Ring opening of these functionalized azlactones then provides access to α,α-disubstituted amino acids (R ≠ H). Such modified amino acids are important building blocks in peptide chemistry as their introduction into a peptide strand can induce helical structures as exemplified by the alanine analog, Aib (aminoisobutyric acid) [18–25].

Similar to the above-mentioned transformations, the Hartwig group reported on the Pd-catalyzed α-arylation of *N*-protected amino acids and azlactones [26,27]. The α-arylation of ketones was initially discovered independently by the groups of Buchwald [28], Hartwig [29] and Miura [30], and has since been intensively studied by the two former groups and extended to other enolizable molecules such as esters, nitriles and malonates [31–34]. Furthermore, we and others have proven the feasiblility of a carbonylative version of these reactions giving access to 1,3-dicarbonyl and related structures [35–45]. Carbonylation chemistry is mainly based on three-component couplings (CO, nucleophile and electrophile) [46–50], however, examples on four-component carbonylative couplings have also been reported [51–62], particularly from the Arndtsen group [63–73].

In this communication, we present a formal four-component coupling approach for accessing α-acylated amino acid derivatives involving the Pd-catalyzed carbonylative α-arylation of azlactones followed by an ensuing alcoholysis [74,75]. This was enabled with the aid of *ex situ* generated CO in a two-chamber system (Scheme 1d) [76,77]. The transformation proved compatible with a wide array of aryl iodides, but also different nucleophiles and azlactones could be employed. Mechanistic insight into the transformation, as

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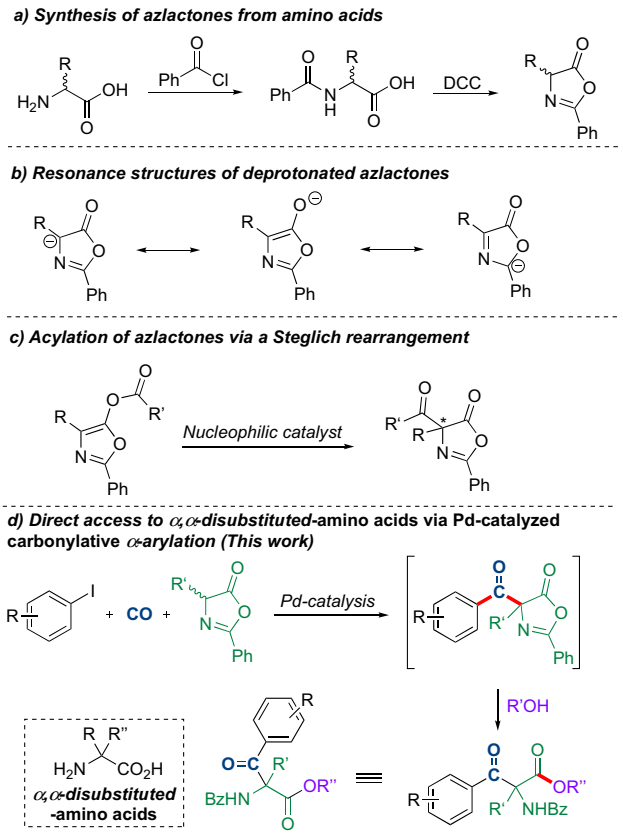


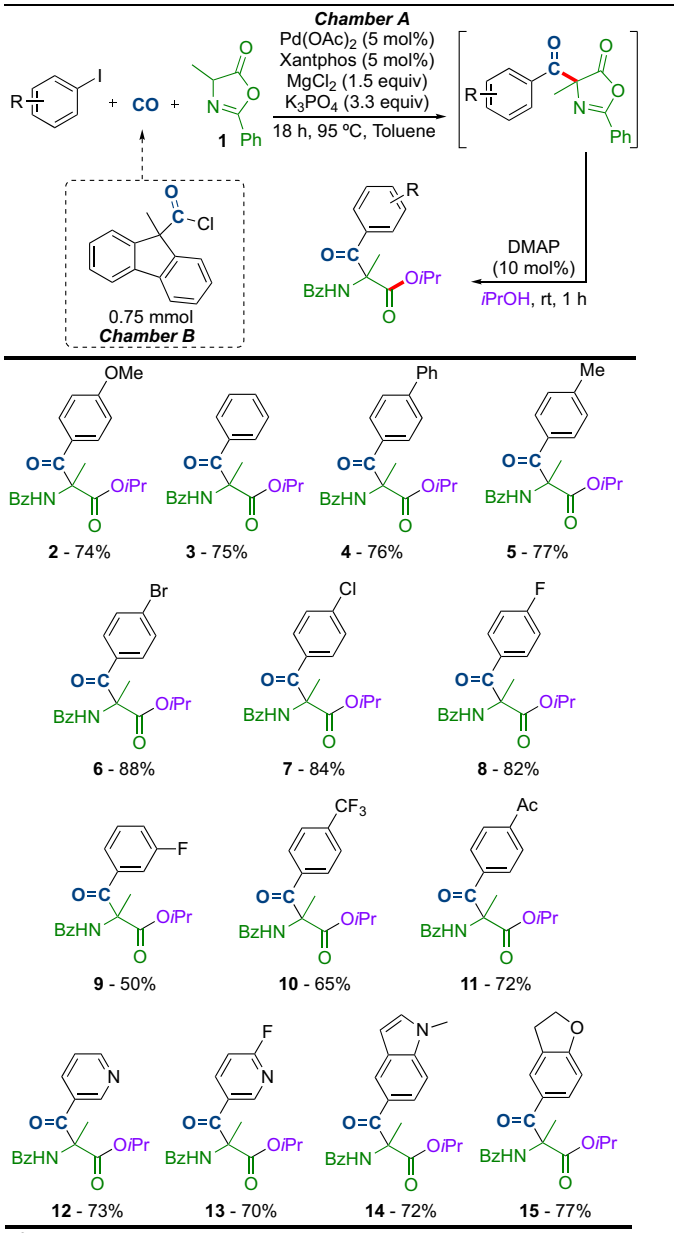
Scheme 1. Preparation of azlactones and their inherent reactivity.

well as isotope labeling (^{13}C and ^{2}H) and derivatization of the resulting doubly protected α,α-disubstituted amino acid is presented.

A brief optimization of the reaction conditions revealed K_3PO_4 as the base of choice using 4-iodoanisole as the electrophile and 4-methyl-2-phenyloxazolinone **1**, the azlactone derived from alanine. Attempting to utilize the corresponding aryl bromide resulted in low conversion (<30%) and a messy mixture of products was observed when employing aryl triflates or aryl fluorosulfates. $MgCl_2$ proved crucial for suppressing the competing *O*-acylation [45,78], and Xantphos was the optimal ligand for this transformation. Because of the inherent instability of the *C*-acylated azlactone on silica gel, the reaction mixture was filtered over a Celite pad followed by solvent removal. An ensuing alcoholysis was then performed on the remaining residue generating the desired α,α-disubstituted amino acid **2** after flash column chromatography.

With the optimal reaction conditions in hand for the transformation (For details, see Supporting Information), a range of aryl iodides were evaluated as potential coupling partners (Table 1). Employing electron-neutral aryl iodides, such as iodobenzene or 4-methyl/phenyl derivatives maintained the good yield of the transformation as illustrated with amino acids **3**–**5**. Halides such as chloride, bromide and fluoride remained untouched as for **6**–**9**, which is an important feature as these groups are useful chemical handles for further derivatization of the compounds either through transition metal catalysis or direct S_NAr. Electron-withdrawing groups such as a trifluoromethyl- or an acetyl group did not hamper the efficiency of the reaction (compounds **10** and **11**). Iodinated heterocycles such as pyridines, an indole and a dihydrofuran could be successfully employed as electrophiles as well, providing **12**–**15** in good yields. *Ortho*-substituted aryl iodides such as 1-chloro-2-iodobenzene and 1-iodo-2-methoxybenzene suffered from low

Table 1
Scope of aryl iodides as the coupling partner.[a]



[a] General conditions: Chamber A: Aryl iodide (0.36 mmol), **1** (98.0 mg, 0.55 mmol, 1.5 equiv), $Pd(OAc)_2$ (4.0 mg, 0.018 mmol, 5 mol%), Xantphos (4.6 mg, 0.018 mmol, 5 mol%), $MgCl_2$ (51.4 mg, 0.55 mmol, 1.5 equiv), K_3PO_4 (252.0 mg, 1.18 mmol, 3.3 equiv) and toluene (3.0 mL). Chamber B: COgen (131.1 mg, 0.54 mmol), $Pd(dba)_2$ (15.5 mg, 0.027 mmol, 5.0 mol%), $HBF_4P(tBu)_3$ (7.8 mg, 0.027 mmol, 5.0 mol%), Cy_2NMe (230 μL, 1.08 mmol, 2.0 equiv) and toluene (2.0 mL). The two-chamber system was heated at 95 °C for 16 h. DMAP (4.4 mg, 0.036 mmol, 10 mol%) and isopropanol (2.0 mL) were added to Chamber A after the reaction mixture had been cooled down and stirred at room temperature for 1 h. All yields are isolated after column chromatography, and are averages of two independent runs.

conversion, whereas having a 2-pyridyl group present did not provide any product formation (results not shown).

Having investigated the role of the electrophile, attention was then turned towards the nucleophilic counterparts (Table 2). The use of azlactones possessing different side chains side-chain being derived from leucine, methionine and phenylalanine proved also to be successful for this chemistry (**16**–**18**). The ring-opening step was not limited to isopropanol as other nucleophiles such as benzyl amine and phenol could be employed as illustrated with the α, α-disubstituted amino acids **19** and **20**.