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Very Important Publication

Direct Access to α,β-Unsaturated γ-Lactams via Palladium-Catalysed Carbonylation of Propargylic Ureas

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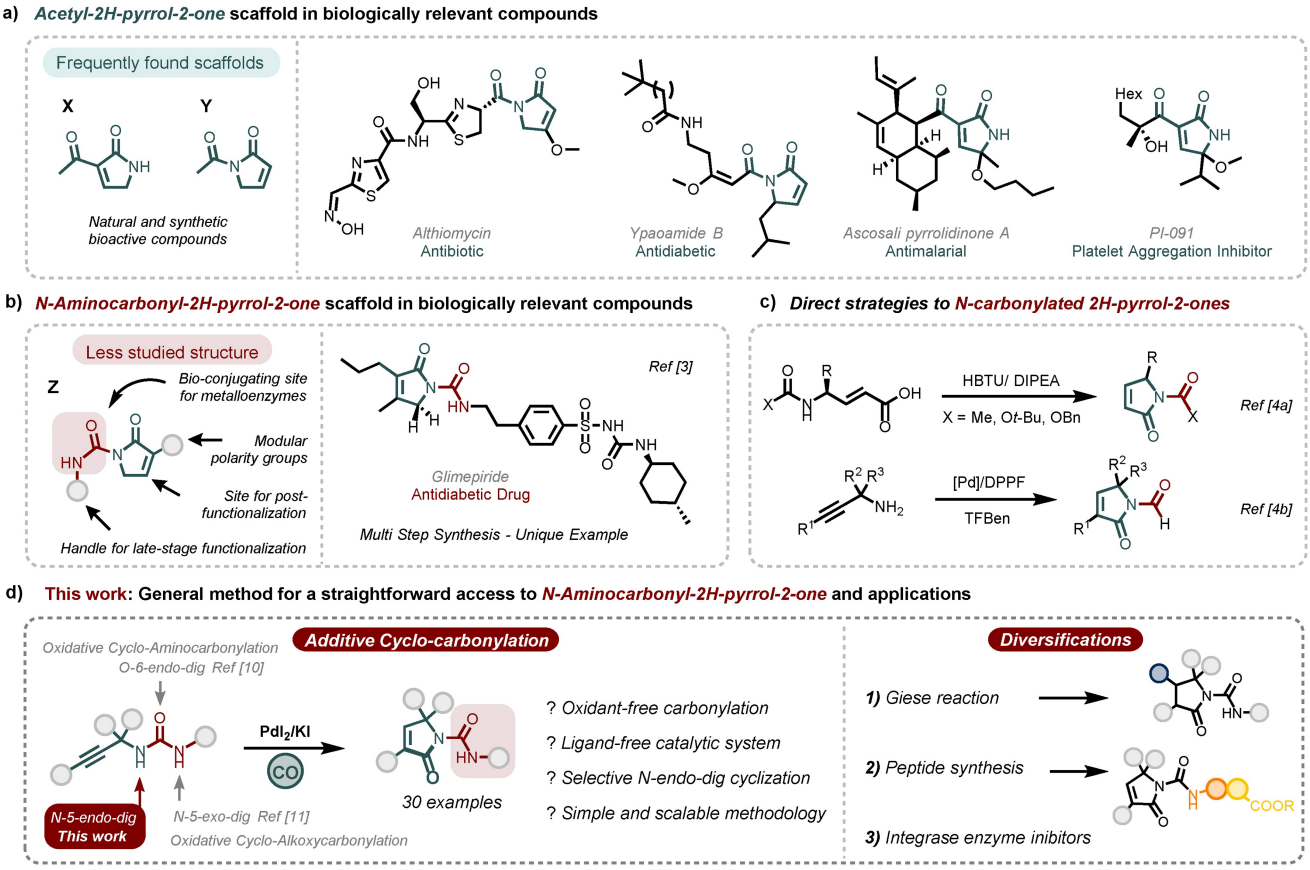
Abstract: Additive carbonylations typically necessitate strong nucleophiles, such as alcohols or amines. In this study, we carbonylated a poorly nucleophilic urea, under oxidant-free conditions. Our straightforward carbonylative strategy enables access to versatile α,β-unsaturated γ-lactams featuring an aminocarbonyl fragment, utilizing readily available propargylic ureas as starting materials. The employment of the PdI_2/KI catalytic system allowed complete regioselectivity (*5-endo-dig*), high functional group tolerance, broad substrate scope as well as operational simplicity (oxidant-free, organic ligand-free and base-free protocol). The synthetic utility of these γ-lactams is showcased through late-stage functionalizations, such as Giese reactions and peptide couplings.

Keywords: Palladium; Carbonylation; γ-lactams; Propargylic ureas; *5-Endo-dig* cyclization

Introduction

Beyond common γ-lactams, α,β-unsaturated-γ-lactams stand out as a crucial structural core for a vast array of natural and synthetic products boasting a range of significant properties.[1] The introduction of a carbonyl moiety at either the α-position (**X**) or the adjacent nitrogen atom (**Y**) further enhances their biological activity, as evidenced by the abundance of natural products incorporating this structural motif (Scheme 1a).[2] Like so, *Althiomycin* is an antibiotic effective against Gram-positive and Gram-negative bacteria,[2a] *Ypaoamide B* is active in the treatment of Type 2 diabetes mellitus (T2DM),[2b] *Ascosati pyrrolidone A* is an antimalarial drug[2c], and *PI-091* has shown to inhibit thrombus formation by reducing platelet aggregation[2d]. Compared to structures **X** and **Y**, the α,β-unsaturated-γ-lactams featuring an aminocarbonyl moiety on nitrogen (**Z**) offer multiple sites for synthetic and bioconjugation purposes (Scheme 1b). In particular, compared with its most common analogues, the exocyclic ureic nitrogen may be a useful handle for post-functionalization. Despite their potential, **Z** remains a relatively unexplored scaffold. To our knowledge, the antidiabetic drug *Glimepiride*, synthesized through a tedious multistep process, is the sole



Scheme 1. a) Natural and synthetic active molecules containing acetyl-2*H*-pyrrol-2-one scaffold; b) Less studied *N*-aminocarbonyl-2*H*-pyrrol-2-one platform; c) Direct strategies to *N*-carbonylated 2*H*-pyrrol-2-ones; d) *This work*.

reported example containing this structure.[3] Moreover, direct strategies to *N*-carbonylated 2*H*-pyrrol-2-ones are similarly rare (Scheme 1c).[4] The synthetic utility of these compounds is further supported by related reactions, including HBTU-mediated cyclization of *N*-protected-(*E*)-α,β-unsaturated γ-amino acids to the corresponding *N*-acylated *2H*-pyrrol-2-ones under basic conditions,[4a] and the direct synthesis of 2-oxo-2,5-dihydropyrroles from propargyl amines and TFBen (benzene-1,3,5-triyl triformate) under palladium catalysis.[4b] While many valuable synthetic methodologies for the synthesis of α,β-unsaturated-γ-lactams are available,[5] direct access to structure **Z**, characterized by the essential carbonyl function at the nitrogen, is missing.

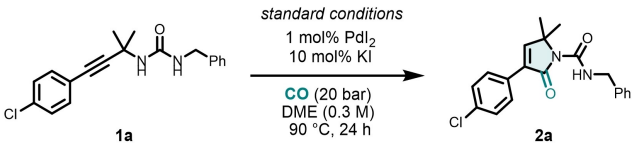
Carbonylation with carbon monoxide represents a common tool to introduce a carbonyl moiety to an organic substrate starting from a simple and readily available C1 source.[6] In this context, palladium-catalyzed carbonylation reactions remain crucial in synthesizing carbonyl-containing compounds, such as esters, amides, carbamates and ureas.[7] Building upon our prior research in carbonylation,[8] we present a straightforward and reliable method for synthesizing α,β-unsaturated-γ-lactams with an aminocarbonyl moiety (Scheme 1d) under PdI_2/KI catalysis[7c] starting from easily accessible propargylic ureas. The reaction provides target compounds in good to quantitative yields and excellent regioselectivity without any organic ligands or tedious work-up. Among the established types of carbonylation reactions,[7d] the additive carbonylation offers several advantages such as complete atom economy and no requirement for oxidizing agents or bases. Importantly, this strategy allows the direct activation of the low nucleophilic ureic nitrogen[9] towards *N-5-endo-dig* cyclocarbonylation in place of the previously reported *O-6-endo-dig*[10] and *N-5-exo-dig*[11] pathways. Examples of late-stage functionalization, such as the Giese reaction and peptide synthesis, demonstrate the synthetic versatility of this new class of products (Scheme 1d, right). Finally, we include a preliminary in silico and experimental investigation of these compounds as potential new anti-HIV agents.[12]

Results and Discussion

We initiated the optimization process by selecting propargylic urea **1a** as the starting material for tuning reaction parameters. After an extensive optimization study (see SI, Table S1), we identified the standard conditions for the reaction. When compound **1a** was subjected to a reaction with CO (20 atm, autoclave) in the presence of PdI_2 (1 mol%) and KI (10 mol%) in DME (0.3 M) at 90 °C for 24 hours, we observed the complete conversion to the α,β-unsaturated-γ-lactam derivative **2a** (Table 1, entry 1). The compound was directly purified *via* column chromatography and fully characterized (see SI). A comparable result was achieved by using K_2PdI_4 as a pre-catalyst (Table 1, entry 2). Lowering the CO pressure to 10 atm resulted in a sharp drop in yield of **2a** (24%, entry 3, Table 1), while no product formation was observed by conducting the reaction under atmospheric pressure of carbon monoxide (Table 1, entry 4). Reducing the reaction temperature affected the transformation efficiency (Table 1, entry 5), while shortening the reaction time to 16 hours had little impact (Table 1, entry 6). However, to guarantee complete conversion of the starting materials during the reaction scope investigation, we decided to maintain 24 hours as the optimized reaction time.

Solvent screening revealed that MeCN was not suitable for this reaction (Table 1, entry 7). Conversely, DMF, toluene, and DME proved to be interchangeable, offering flexibility in solvent choice (Table 1, entries 8 and 9). When PdI_2 was employed without KI, **2a** was formed in sharply reduced 60% yield, underlying the importance of the iodide additive for the process (Table 1, entry 10). Finally, to demonstrate the inertness of the metallic autoclave walls, the reaction was performed in the absence of the catalyst. Under these conditions, **2a** was not detected even in traces (Table 1, entry 11).

Table 1. Optimization study and control experiments.[a]

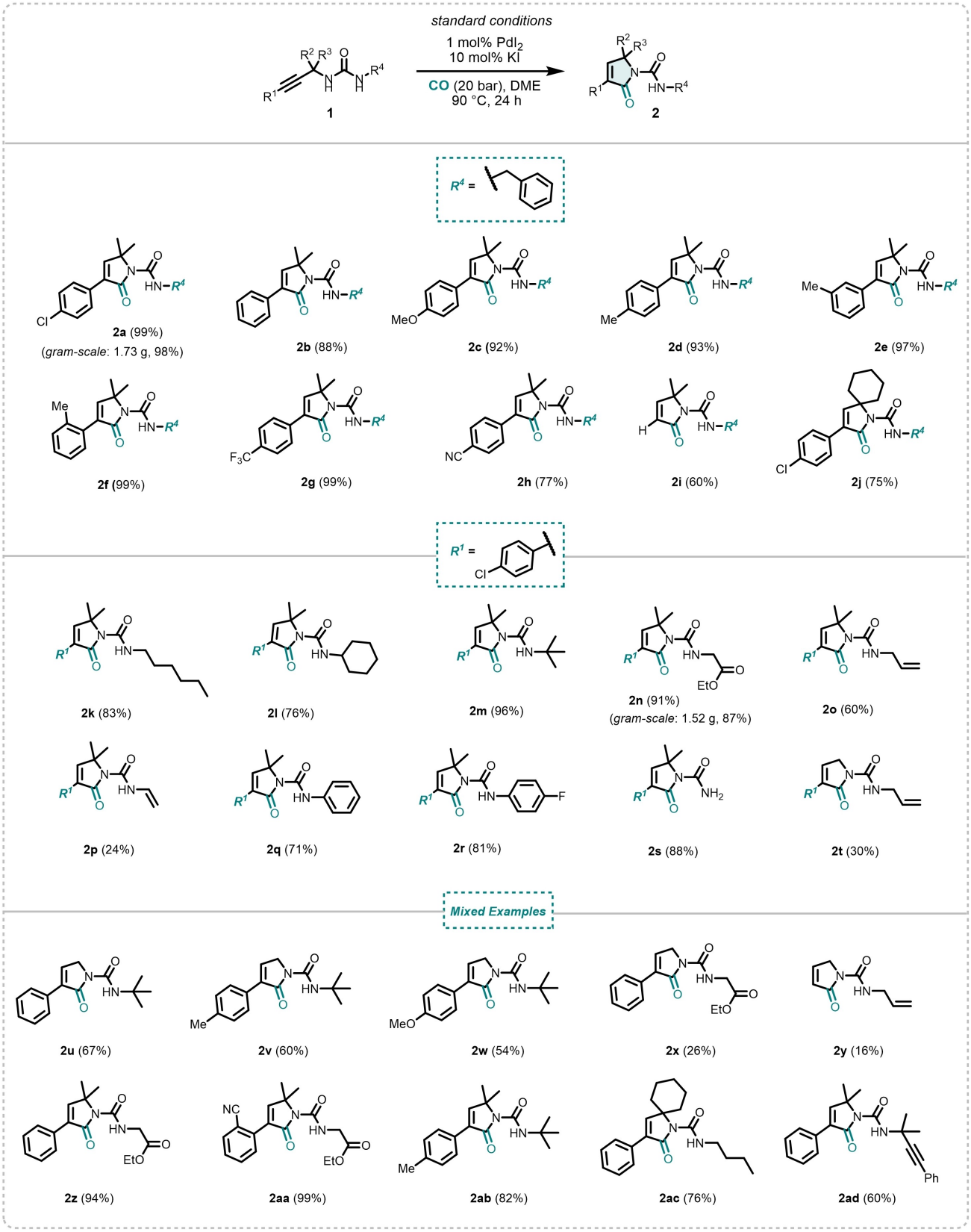


Entry	Deviation from standard conditions	Yield (%) of **2a**[b]
1	none	100
2	1 mol % K_2PdI_4	100
3	10 bar	24
4	1 bar	n.d.
5	70 °C	73
6	16 h	98
7	MeCN	50
8	Toluene	98
9	DMF	97
10	no KI	60
11	no PdI_2, no KI	n.d.

[a] Reaction conditions: **1a** (0.5 mmol, 1 equiv.), PdI_2 (1 mol %) and KI (10 mol %) in DME (0.3 M), CO (20 bar), 90 °C, 24 h.

[b] Determined by ^1H NMR using trichloroethylene as external standard.

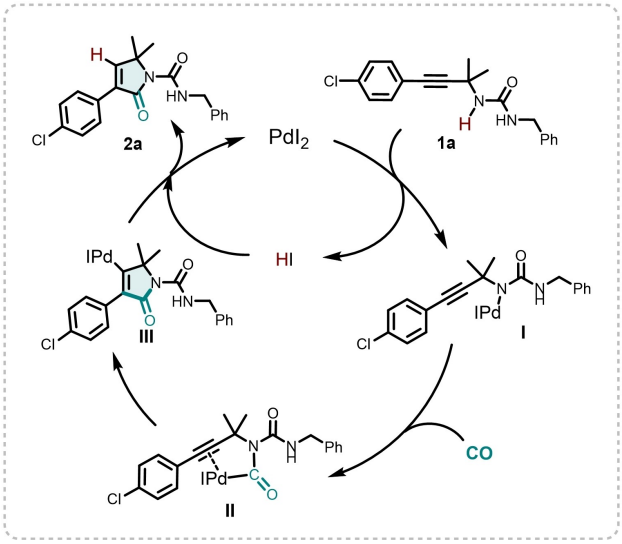
To assess the versatility of our protocol, we investigated the reaction scope with a variety of substituted propargyl ureas **1** under the established reaction conditions (Scheme 2). We first studied the effect of R^1 substituent, installed by Sonogashira coupling on terminal triple bond (see SI for details). The Ph-substituted substrate underwent carbonylation affording 2-pyrrolidone **2b** in 88% yield. The substrates bearing electron rich arenes with OMe and Me groups in *para* position led to clean formation of **2c** and **2d**. Similarly, the reaction displayed high compatibility with Me substituent at the *meta* (**2e**) and *ortho* (**2f**) positions of the aromatic ring. Electron-withdrawing functions such as CF_3 and CN afforded the corresponding carbonylated products **2g** and **2h** in 99 and 77% yield, respectively. In contrast, the carbonylation of a propargyl urea containing an unsubstituted ethynyl moiety afforded **2i** with a satisfactory yield of 60%. The azaspiro-carboxamide scaffold **2j** was obtained in good 75% yield. The second series of products was obtained preserving *p*-chlorobenzene (R^1) at the alkyne function (Scheme 2, $R^1 = p\text{-Cl-}C_6H_4$). Aliphatic groups bonded to the nitrogen were entirely tolerated under standard conditions. Products **2k**, **2l**, and **2m** were obtained in good to excellent yields (76–96%, Scheme 2), demonstrating tolerance for increased steric hindrance without compromising the reaction efficiency. The presence of an ester group on the substrate proved compatible with the reaction, as demonstrated by the 91% yield of product **2n** derived from the glycine-containing precursor. A gram-scale reaction has been performed for the synthesis of **2n** which afforded 87% yield of the product. Interestingly, the substrate bearing allylic moiety was smoothly converted into **2o** with a good yield of 60%. On the other hand, only a low yield of 24% was obtained for **2p** featuring a vinyl moiety. Substrates bearing an aryl ring on the terminal ureic nitrogen underwent prompt conversion into products **2q** and **2r** with 71 and 81% yield, respectively. Surprisingly, the unprotected NH_2 group on the substrate was perfectly tolerated, leading to lactam **2s** in excellent yield (88%). The pivotal role of the Thorpe-Ingold effect was verified as product **2t** was formed in lower yield (30%) compared to other substrate with *gem* dimethyl substituents (**2o**). Pushing the boundaries of the reaction, we employed substrates containing a *tert*-butyl group at R^4 (**2u–w**) despite lacking substituents at R^2 and R^3 positions. These substrates were successfully carbonylated, affording



Scheme 2. Scope of the palladium-catalyzed carbonylation of propargyl urea **1** to γ-lactam **2a**.

the desired γ-lactams in moderate to good yields (54–67%). We attribute the low yield of product **2 x** and **2 y** (26 and 16%) to the above-mentioned *gem*-dialkyl effect.[13] In contrast, Thorpe-Ingold effect promoted the formation of the glycine-containing compounds **2 z** and **2 aa** with excellent yields. As expected, the substrate bearing tolyl in R^1 and *tert*-butyl in R^4 was highly prone to carbonylation, providing **2 ab** in 82% yield. Spiro compound **2 ac** was obtained in 76% yield, while symmetric urea was successfully subjected to the carbonylative protocol and afforded mono carbonylated product **2 ad** in 60% yield after 24 h of reaction time. It's worth noting that a subsequent second carbonylation turns out to be more challenging.

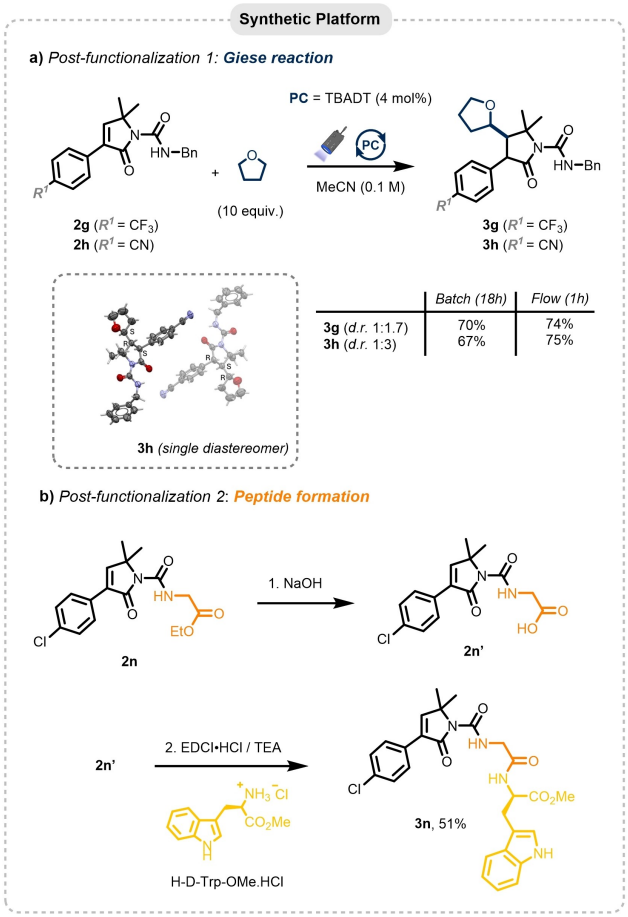
Although the exact mechanism of the reaction is to date unclear, based on the existing knowledge on carbonylation and our expertise in PdI_2/KI-catalyzed carbonylation reactions,[7c,8,10,11] we propose the following mechanism for the formation of compound **2 a** (Scheme 3). Initially, the palladation of the nitrogen of **1 a** leads to the aminopalladium intermediate **I**, stabilized by a possible intramolecular triple bond coordination (additional anionic iodide ligands are omitted for clarity). Then, coordination of CO followed by migratory insertion affords the carbamoylpalladium complex **II**, which undergoes *5-endo-dig* cyclization to **III**. Finally, electrophilic displacement by HI on **III** affords **2 a** and PdI_2, ready to restart a new catalytic cycle. This pathway aligns well with the complete regioselectivity of the process. An alternative pathway for the formation of **2 a**, which would involve the *in situ* generation of a Pd–H species,[14] appears to be less likely, although its potential contribution cannot be ruled out. Ongoing studies are aimed at shedding light on the reaction mechanism.



Scheme 3. Proposed catalytic cycle for the formation of **2**.

We further demonstrated the synthetic utility of *N*-aminocarbonyl α,β-unsaturated-γ-lactams through a series of site-selective post-transformations (Scheme 4).

The reactivity of the unsaturated fragment has been intensively studied through reactions such as hydrogenation, epoxidation, and pyrrole synthesis.[5a] In this work, compound **2 g** and **2 h** have been employed for the first time as SOMOphile acceptor in the Giese reaction,[15] leading to highly functionalized γ-lactams **3 g** and **3 h** *via* photocatalyzed HAT reaction with 70 and 67% yield, respectively (Scheme 4a). Flow conditions were found to improve yields and significantly reduce reaction time. Importantly, among four possible diastereoisomers, only two were observed in 1:1.7 and 1:3 molar ratio, respectively for **3 g** and **3 h**, from ^{1}H NMR spectra. In addition, a single-crystal X-ray diffraction, reporting the configuration of the stereocenters, has been obtained for one of them (Figure S6, SI). Secondly, compound **2 n** containing a glycine arm has been converted into the corresponding acid by hydrolysis with NaOH and further coupled with D-



Scheme 4. a) Post-functionalization through Giese reaction *via* photocatalyzed HAT; b) Post-functionalization with the D-tryptophan methyl ester.

tryptophan methyl ester, allowing to obtain di-peptide **3 n** in 51% isolated yield (Scheme 4b, see SI).

From a biological standpoint, selected substrates have been previously tested for their activity against HIV infection and were found to be effective.[12] This activity has now been confirmed for two of the newly reported derivatives, namely **2u** and **2y** (Table S5, SI). To explore their potential biomolecular target, an in silico "target fishing" approach was employed, using experimentally determined structures of eight different anti-HIV molecular targets bound to known inhibitors. (Table S6, SI) The computational studies strongly suggested HIV integrase as the molecular target for compounds **2u** and **2y** (Scheme S1, SI). These findings were further validated through biological testing, which confirmed HIV integrase inhibition using a cell-free colorimetric assay, corroborating the predictions from the in silico studies (Table S5, SI). Noteworthy, both pyrrole carboxamide-based compounds exhibited low cytotoxicity at concentration that inhibit HIV integrase, with **2y** showing a high selectivity index (S.I.), making it a promising candidate for further modifications meant to develop more potent and selective compounds.

Conclusion

In conclusion, we have reported the palladium-catalyzed carbonylative synthesis of polyfunctionalized α,β-unsaturated-γ-lactams from propargyl ureas. The reaction proceeds through regioselective carbonylation of the poorly nucleophilic ureic nitrogen *via* 5-*endo*-*dig* cyclization. The methodology features high functional group tolerance, broad substrate scope as well as operational simplicity (no oxidant, no organic ligand, no base, no work up). Furthermore, *N*-aminocarbonylated 2*H*-pyrrol-2-ones demonstrate synthetic versatility, serving as valuable building blocks for both Giese reactions and controlled dipeptide synthesis. Additionally, the preliminary results regarding their anti-HIV activity, specifically targeting HIV integrase enzyme, demonstrate the potential of these molecules as high-impact substrates for future pharmaceutical applications.

Experimental Section

General Procedure for the Carbonylation of Propargyl Ureas 1 to γ-Lactam 2

A 45 mL stainless steel autoclave equipped with a magnetic stirrer was charged with propargyl urea **1** (1 equiv., 1 mmol), PdI_2 (1 mol%) and KI (10 mol %) in dimethoxyethane (0.3 M). The autoclave was then purged with N_2 and sealed. Carbon monoxide (15 bar) was charged and evacuated 2 times to obtain an oxygen-free atmosphere and eventually charged again with CO (20 bar). The autoclave was put into an oil bath heated to 90 °C, and the reaction mixture was stirred for 24 h. The oil bath was then removed, and the autoclave was cooled down to room temperature. CO was carefully released, and the reaction mixture was concentrated under reduced pressure. The resulting crude was purified by column chromatography on silica gel using hexane/EtOAc mixtures as eluent to afford γ-lactam **2**.

X-Ray Data

CCDC 2381559 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/structures.

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RESEARCH ARTICLE

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Adv. Synth. Catal. **2024**, *366*, 1–8

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