A Stereoselective, Multicomponent Catalytic Carbonylative Approach to a New Class of α,β-Unsaturated γ-Lactam Derivatives

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Abstract: We report a stereoselective, multicomponent catalytic carbonylative approach to a new class of α,β-unsaturated γ-lactam derivatives with potential biological activity, that are, alkyl (Z)-2-(2-oxopyrrolidin-3-ylidene)acetates. Our method is based on the catalytic assembly of readily available building blocks, namely, homopropargylic amines, carbon monoxide, an alcohol, and oxygen (from air). These simple substrates are efficiently activated in ordered sequence under the action of a very simple catalytic system, consisting of PdI2 in conjunction with KI to give the γ-lactam products in 47–85% yields. Carbonylation reactions are carried out at 100 °C for 2–5 h under 40 atm of a 4:1 mixture of CO-air, with 0.5–5 mol% of PdI2 and 5–50 mol% of KI.

Keywords: carbonylation; γ-lactams; heterocycles; homogeneous catalysis; homopropargylic amines; multicomponent reaction; oxidative carbonylation; palladium; pyrrolidinones; stereoselective synthesis

1. Introduction

Carbonylation reactions represent an excellent approach for the direct synthesis of carbonyl compounds using the simplest and readily available C-1 source, that is, carbon monoxide [1–5]. CO is produced industrially starting from petroleum hydrocarbons, natural gas, and coal, and, in the future, a growing amount of carbon monoxide is also expected to be available from renewable feedstocks, such as biowastes and CO2 [6].

In this work, a stereoselective, multicomponent catalytic carbonylative approach to a new class of α,β-unsaturated γ-lactam derivatives, that are, alkyl (Z)-2-(2-oxopyrrolidin-3-ylidene)acetates 2, is presented. The synthetic approach is based on the use of a particularly simple catalytic system, consisting of PdI2 in conjunction with KI [7,8], for the catalytic activation of very simple starting materials (homopropargylic amines 1, carbon monoxide, an alcohol, and oxygen; Scheme 1).

The (Z)-2-(2-oxopyrrolidin-3-ylidene)acetate core has been previously obtained by Rh(I)-catalyzed enyne cycloisomerization [9], intramolecular palladium-catalyzed allylic alkylation of phosphonoacetamides followed by Horner-Wadsworth-Emmons olefination.
with ethyl glyoxalate [10], condensation of dimethyl itaconate with glycine methyl ester [11], and the reaction of 2-benzyl 1-(2,2,2-trichloroethyl) (Z)-4-((dimethylamino)methylene)-5-oxopyrrolidine-1,2-dicarboxylate with 2,2,2-trichloroethoxy carbonyl chloride [12]. To the best of our knowledge, however, no method has been reported so far to synthesize the γ-lactam derivatives 2 disclosed in this work.

Interestingly, heterocyclic compounds bearing the strictly related 2-(2-oxopyrrolidin-3-yl)acetate moiety (with a saturated exocyclic carbon-carbon bond) have been reported to exhibit different biological activities, including peptidomimetic inhibitory effect [13], and anti-hepatitis B [14], anti-stroke [15], and anti-thrombotic [16] activity. Therefore, the disclosure of an efficient method for the synthesis of 2 can be of interest for the development of novel bioactive small molecules. In particular, the target compounds incorporate into their structure the 2-(2-oxopyrrolidin-3-ylidene)acetate moiety with an exocyclic double bond, which, as a Michael acceptor group, may react with biological thiols (e.g., glutathione, cysteine) [17], thus inducing diverse biological activities. For this purpose, a biochemical and pharmacological investigation on the cytotoxicity and antiproliferative activity of 2 in tumor cell lines is being carried out in our laboratories, and the first noteworthy results will be reported in due course.

2. Results and Discussion

The synthetic method developed in our work for the preparation of new alkyl (Z)-2-(2-oxopyrrolidin-3-ylidene)acetates derivatives 2 is based on the oxidative carbonylation of readily available 3-yn-1-amines (homopropargylic amines) 1 carried out with the very simple PdI₂/KI catalytic system (Scheme 1).

Our initial experiments were based on the use of N-(but-3-yn-1-yl)aniline 1a as model substrate to assess the feasibility of our hypothesis and to optimize the carbonylation conditions. When 1a was allowed to react with CO, MeOH, and O₂ (from air), in MeOH as the solvent (0.04 mmol of 1a per mL of MeOH) under 40 atm of a 4:1 mixture of CO-air at 100 °C and in the presence of PdI₂ (5 mol%) and KI (0.5 equiv), after 2 h the GLC-MS analysis of the reaction mixture evidenced a complete substrate conversion and the formation of a product, whose MS spectrum was compatible with the desired γ-lactam derivative 2a. This compound was then isolated from the mixture (74% based on starting 1a, Table 1, entry 1) and fully characterized by IR, HNMR, and 13CNMR spectroscopies and by XRD analysis, which confirmed the structure corresponding to methyl (Z)-2-(2-oxo-1-phenylpyrrolidin-3-ylidene)acetate 2a (Figure 1; see the Supplementary Materials for full XRD data).

With the aim of obtaining a higher yield of 2a, we then changed the reaction parameters, such as the KI amount, substrate concentration, temperature, and pressure. After this brief optimization study (Table 1, Entries 2–10), 2a was obtained in 85% isolated yield working under the same conditions as those of entry 1, but with a substrate concentration of 0.1 mmol/mL of MeOH (Table 1, entry 7, and Table 2, entry 1). Good yields were still obtained when the process was carried out with lower catalyst loadings (72% yield with 1 mol% of PdI₂, and 64% yield with 0.5 mol% of PdI₂; Table 2, entries 2 and 3, respectively). The use of EtOH instead of MeOH did not cause a significant change in product yield, the corresponding ethyl ester 2a′ being obtained in 82% yield with 5 mol% PdI₂ (Table 2, entry 4). On the other hand, more hindered and less nucleophilic isopropanol led to a lower
yield of the corresponding ester \(2a''\) (72%; Table 2, entry 5). With tert-butanol, the yield of \(2a''\) was 33% (Table 2, entry 6), which, however, could be improved to 54% working under more diluted conditions (Table 2, entry 7).

**Table 1. Optimization of carbonylation conditions.**

| Entry | \(\text{PdI}_2/\text{KI}/1\text{a Molar Ratio}\) | \(\text{Concn of } 1\text{a}\) | \(T(°C)\) | \(t(h)\) | \(P_{\text{CO}}(\text{atm})\) | \(P_{\text{air}}(\text{atm})\) | Yield (%) |
|-------|-------------------------------------------|----------------|--------|------|----------------|----------------|---------|
| 1     | \(1/10/20\)                               | 0.04           | 100    | 2    | 32              | 8              | 74      |
| 2     | \(1/5/20\)                                | 0.04           | 100    | 2    | 32              | 8              | 65      |
| 3     | \(1/2/20\)                                | 0.04           | 100    | 2    | 32              | 8              | 55      |
| 4     | \(1/10/20\)                               | 0.04           | 100    | 2    | 48              | 12             | 66      |
| 5     | \(1/10/20\)                               | 0.04           | 100    | 2    | 16              | 4              | 67      |
| 6     | \(1/10/20\)                               | 0.02           | 100    | 2    | 32              | 8              | 59      |
| 7     | \(1/10/20\)                               | 0.10           | 100    | 2    | 32              | 8              | 85      |
| 8     | \(1/10/20\)                               | 0.04           | 80     | 2    | 32              | 8              | 55      |
| 9     | \(1/10/20\)                               | 0.04           | 100    | 1    | 32              | 8              | 42 d    |
| 10    | \(1/10/20\)                               | 0.04           | 100    | 8    | 32              | 8              | 33      |

*All reactions were carried out in MeOH. Unless otherwise noted, substrate conversion was quantitative in all cases. b Mmol of \(1\text{a}\) per mL of MeOH. c Isolated yield based on starting \(1\text{a}\). d Substrate conversion was 85%.*

![Figure 1. Molecular structure of methyl (Z)-2-(2-oxo-1-phenylpyrrolidin-3-ylidene)acetate \(2\text{a}\). The figure shows the atom labelling scheme for non-H atoms and displacement ellipsoids at the 50% probability level.](image)

Our next step was to verify the generality of the process using other differently substituted homopropargylic amines \(1\text{b–n}\) (Table 2, entries 8–27). Very good results were consistently obtained with all the tested \(N\)-aryl-substituted substrates \(1\text{b–1k}\), bearing electron-withdrawing as well as electron-donating substituents (entries 8–20). The structure of another representative product, methyl (Z)-2-(1-(4-chlorophenyl)-2-oxopyrrolidin-3-ylidene)acetate \(2\text{b}\), was confirmed again by XRD analysis (Figure 2; see the Supplementary Materials for full XRD data). We assessed the possibility to work with a lower catalyst loading (1 mol% of PdI\(_2\)) also for substrates \(1\text{b}\) (Table 2, entry 9), \(1\text{c}\) (Table 2, entry 11), and \(1\text{e}\) (Table 2, entry 14), still with satisfactory results. In fact, the yields of products \(2\text{b}, 2\text{c},\) and \(2\text{e}\) were only slightly inferior with respect to those obtained with 5 mol% of PdI\(_2\) (Table 2; compare entries 9, 11, and 14 with entries 8, 10, and 13, respectively).
Table 2. Multicomponent PdI$_2$/KI-catalyzed carbonylative synthesis of alkyl (Z)-2-(2-oxopyrrolidin-3-ylidene)acetates 2$^{a,b}$.

![Chemical Reaction]

| Entry | 1 | ROH | PdI$_2$/KI Molar Ratio | Substrate Concentration $^c$ | Time (h) | 2 | Yield of 2 (%) $^d$ |
|-------|---|-----|------------------------|-----------------------------|----------|---|-------------------|
| 1     | 1a | MeOH| 1/10/20                | 0.1                         | 2        | 2a | 85               |
| 2     | 1a | MeOH| 1/10/100               | 0.1                         | 2        | 2a | 72               |
| 3     | 1a | MeOH| 1/10/200               | 0.1                         | 2        | 2a | 64               |
| 4     | 1a | EtOH| 1/10/20                | 0.1                         | 2        | 2a | 82               |
| 5     | 1a | $^{t}$PrOH          | 1/10/20                | 0.1                         | 2        | 2a | 72               |
| 6     | 1a | $^{t}$BuOH          | 1/10/20                | 0.1                         | 2        | 2a | 33               |
| 7     | 1a | $^{t}$BuOH          | 1/10/20                | 0.04                        | 2        | 2a | 54               |
| 8     | 1b | MeOH| 1/10/20                | 0.1                         | 2        | 2b | 77               |
| 9     | 1b | MeOH| 1/10/100               | 0.1                         | 2        | 2b | 72               |
Table 2. Multicomponent PdI$_2$/KI-catalyzed carbonylative synthesis of alkyl (aromatic) ylidene)acetates

| Entry | 1             | ROH  | PdI$_2$/KI/1 Molar Ratio | Substrate Concentration | Time (h) | 2                    | Yield of 2 (%) $^d$ |
|-------|---------------|------|--------------------------|-------------------------|----------|----------------------|---------------------|
| 10    | $^{1\text{Pr}}$-NH-CH$_2$CH$_3$ | MeOH | 1/10/20                  | 0.1                     | 2        | 2                    | 74                  |
| 11    | 1c            | MeOH | 1/10/100                 | 0.1                     | 2        | 2c                   | 72                  |
| 12    | $^{1\text{Bu}}$-NH-CH$_2$CH$_3$ | MeOH | 1/10/20                  | 0.1                     | 2        | 2d                   | 70                  |
| 13    | MeOH          | MeOH | 1/10/20                  | 0.1                     | 2        | 2e                   | 78                  |
| 14    | 1e            | MeOH | 1/10/100                 | 0.1                     | 2        | 2e                   | 75                  |
| 15    | MeOH          | MeOH | 1/10/20                  | 0.1                     | 2        | 2f                   | 77                  |
| 16    | MeOH          | MeOH | 1/10/20                  | 0.1                     | 2        | 2g                   | 78                  |
| 17    | MeOH          | MeOH | 1/10/20                  | 0.1                     | 2        | 2h                   | 82                  |
Table 2. Cont.

| Entry | 1           | ROH | PdI$_2$/KI/1 Molar Ratio | Substrate Concentration | Time (h) | 2               | Yield of 2 (%) $^d$ |
|-------|-------------|-----|--------------------------|-------------------------|----------|------------------|---------------------|
| 18    | ![Image](1i.png) | MeOH | 1/10/20                   | 0.1                     | 2        | ![Image](2i.png)  | 70                  |
| 19    | ![Image](1j.png) | MeOH | 1/10/20                   | 0.1                     | 2        | ![Image](2j.png)  | 71                  |
| 20    | ![Image](1k.png) | MeOH | 1/10/20                   | 0.1                     | 2        | ![Image](2k.png)  | 70                  |
| 21    | ![Image](1l.png) | MeOH | 1/10/20                   | 0.1                     | 2        | ![Image](2l.png)  | 50                  |
| 22    | ![Image](1l.png) | EtOH | 1/10/20                   | 0.1                     | 5        | ![Image](2l.png)  | 47                  |
| Entry | 1     | ROH   | PdI₂/KI/1 Molar Ratio | Substrate Concentration | Time (h) | 2               | Yield of 2 (%)<sup>d</sup> |
|-------|-------|-------|-----------------------|-------------------------|----------|------------------|-----------------------------|
| 23    | 1l    | PrOH  | 1/10/20               | 0.1                     | 5        | ![Structure](image) | 48                          |
| 24    | 1l    | MeOH  | 1/10/20               | 0.04                    | 2        | ![Structure](image) | 65                          |
| 25    | ![Structure](image) | MeOH  | 1/10/20               | 0.1                     | 2        | ![Structure](image) | 52                          |
| 26    | 1m    | MeOH  | 1/10/20               | 0.04                    | 2        | ![Structure](image) | 75                          |
| 27    | ![Structure](image) | MeOH  | 1/10/20               | 0.04                    | 5        | ![Structure](image) | 47                          |

<sup>a</sup> Unless otherwise noted, all reactions were carried out in ROH (MeOH, EtOH, iPrOH, or nBuOH) as the solvent at 100 °C under 40 atm (at 25 °C) of a 4:1 mixture of CO-air. <sup>b</sup> Substrate conversion was quantitative in all cases. The formation of heavy products (chromatographically immobile materials) accounted for the difference between product yield and substrate conversion. <sup>c</sup> Mmol of 1 per mL of solvent. <sup>d</sup> Isolated yield based on starting 1.
The carbonylation protocol led to lower γ-lactam yields when starting from N-alkyl substituted substrates, such as N-benzylbut-3-yn-1-amine 11 and N-(1-phenylethyl)but-3-yn-1-amine 1m, as shown in entries 21-23 and 25, respectively. Interestingly, however, the yields of products 21 and 2m could be significantly improved by carrying out the catalytic process under more diluted conditions (entries 24 and 26, respectively). This effect of substrate concentration on the reaction outcome is difficult to rationalize, and we refrain from proposing speculative interpretations. These conditions permitted to achieve an acceptable product yield even when starting from substrate 1n, bearing a highly bulky alkyl group on nitrogen (yield of methyl (Z)-2-(1-(tert-buty1)-2-oxopyrrolidin-3-ylidene)acetate 2n was 47%; Table 2, entry 27).

Based on the existing knowledge on carbonylations [1–5] and on our expertise in PdI2/KI-catalyzed carbonylation reactions [7,8], we can propose the mechanistic pathway shown in Scheme 2 for the formation of (Z)-2-(2-oxopyrrolidin-3-ylidene)acetates 2. Palladation of the nitrogen of 1 initially leads to alkynylaminopalladium intermediate I, stabilized by the intramolecular triple bond coordination (anionic iodide ligands are omitted for clarity). Coordination of CO followed by migratory insertion then affords the carbamoylpalladium complex II, which undergoes intramolecular syn triple bond insertion to yield III, followed by a second insertion of carbon monoxide to give IV. Nucleophilic displacement by ROH on IV finally yields 2 and Pd(0), which is readily oxidized back to catalytically active PdI2 by the action of O2.

Scheme 2. Proposed mechanism for the stereoselective catalytic carbonylative synthesis of alkyl (Z)-2-(2-oxopyrrolidin-3-ylidene)acetates 2 from homopropargylic amines 1.
3. Materials and Methods

3.1. General Experimental Methods

All reactions were analyzed by TLC on silica gel 60 F254 or on neutral alumina and by GLC-MS using a Shimadzu QP-2010 GC–MS apparatus (Shimadzu Italia s.r.l., Milano, Italy) and capillary columns with polymethylsilicone + 5% phenylsilicone as the stationary phase. Column chromatography was performed on silica gel 60 (Merck, 70–230 mesh; Merck Life Science s.r.l., Milano, Italy). Evaporation refers to the removal of solvent under reduced pressure.

Melting points are uncorrected. $^1$H NMR and $^{13}$C NMR spectra were recorded at 25 °C in CDCl$_3$ at 300 MHz and 75 MHz, respectively, with Me$_4$Si as internal standard, using a Bruker DPX Avance 300 NMR Spectrometer (Bruker Italia s.r.l., Milano, Italy); chemical shifts (δ) and coupling constants (J) are given in ppm and in Hz, respectively. IR spectra were taken with a JASCO FT-IR 4200 spectrometer (Jasco Europe s.r.l., Cremella, Lecco, Italy). Mass spectra were obtained using a Shimadzu QP-2010 GC–MS apparatus (Shimadzu Italia s.r.l., Milano, Italy) at 70 eV ionization voltage (normal resolution) and by electrospray ionization mass spectrometry (ESI-MS) (high resolution) with an Agilent 1260 Infinity UHD accurate-mass Q-TOF spectrometer (Agilent Technologies Italia s.p.a., Cernusco Sul Naviglio, Milano, Italy), equipped with a Dual AJS ESI source working in positive ion mode. The fragmentor was set to 175 V.

A flow rate of 8 L/min. The nebulizer was set to 45 psig. The Sheat gas temperature was set at 5% B. Injection volume was 10 μL. A linear gradient from 5% to 95% B; 10–15 min, washing and reconditioning of the column.

3.2. Preparation of Substrates 1a–g and 11–n

N-Substituted 3-yn-1-ylamines 1a–g and 11–n were prepared by the reaction of 3-yn-1-yl tosylates with a primary amine as described below. All starting materials were commercially available (Merck Life Science s.r.l., Milano, Italy) and were used without further purification.

A mixture of the 3-yn-1-yl tosylate (10 mmol; but-3-yn-1-yl tosylate, 2.24 g; pent-4-yn-2-yl tosylate, 2.38 g; hex-5-yn-3-yl tosylate, 2.52 g) and the primary amine (30 mmol; aniline, 2.79 g; 4-chloroaniline, 3.83 g; 4-isopropylaniline, 4.06 g; 4-(tert-butyl)aniline, 4.48 g; 3-bromo-5-methylaniline, 5.58 g; benzylamine, 3.21 g; α-methylbenzylamine, 3.62 g; tert-butylamine, 2.20 g) in MeCN (10 mL) was stirred for 3–24 h (3 h for the synthesis of 1a–g, 11–n or 95:5 CH$_2$Cl$_2$-MeOH (11–m) or Et$_2$O for 1n) (3 × 15 mL). The combined organic layers were washed with brine, dried over K$_2$CO$_3$, filtered, and concentrated under vacuum (30 °C and 100 mbar for 1a–g, 11–m or 30 °C and 850 mbar for 1n). The crude products were purified by column chromatography on silica gel using as eluent hexane–AcOEt from 100:0 to 95:5 (1a–g) or 95:5 CH$_2$Cl$_2$-MeOH (11–m). In the case of 1n, column chromatography with Et$_2$O was followed by fractional distillation to remove the solvent first at 760 mmHg and the under vacuum to collect the pure product.

3.2.1. N-(But-3-yn-1-yl)aniline 1a

Yield: 755.0 mg, 52% based on but-3-yn-1-yl tosylate. Yellow oil. IR (film): $\nu = 3403$ (m, br), 3292 (s, br), 2116 (w), 1604 (s), 1505 (s), 1317 (m), 1262 (m), 751 (m), 693 (m) cm$^{-1}$; $^1$H NMR (CDCl$_3$, 300 MHz): $\delta = 7.25-7.02$ (m, 2 H, aromatic), 6.72 (t, $J = 7.3$, 1H, aromatic), 6.63 (d, $J = 8.1$, 2H, aromatic), 3.92 (s, br, 1H), 3.31 (s, br, 2H), 3.21 (s, br, NCH$_2$CH$_2$), 2.49 (td,
$J = 6.5, 2.5, 2H, NCH_2CH_2), 2.03 (t, J = 2.5, 1H, ≡CH); ^{13}C[^1]H_3NMR (CDCl_3, 75 MHz):
$\delta = 147.6, 129.3 (2C), 117.9, 113.1 (2C), 81.8, 70.0, 42.4, 19.1; GC-MS (EI, 70 eV); m/z = 145
(M^+, 16), 106 (100); HRMS (ESI-TOF) m/z: [(M + H)^+] cald for C_{10}H_{12}N^+: 146.0964; found,
146.0975. The spectroscopic data agreed with those reported [18].

3.2.2. N-(But-3-yn-1-yl)-4-Chloroaniline 1b

Yield: 988.0 mg, 55% based on but-3-yn-1-yl tosylate. Yellow oil. IR (film): ν = 3406 (m,
br), 3296 (s), 2117 (w), 1601 (s), 1504 (s), 1293 (m), 1262 (m), 1089 (m), 817 (s) cm$^{-1}; ^{1}H NMR
(CDCl_3, 300 MHz): δ = 7.16–7.08 (m, 2H, aromatic), 6.58–6.49 (m, 2H, aromatic), 3.95 (s, br,
1H, NH), 3.27 (t, J = 6.6, NCH_2CH_2), 2.48 (td, J = 6.6, 2.6, 2H, NCH_2CH_2), 2.05 (t, J = 2.6, 1H,
≡CH); ^{13}C[^1]H_3NMR (CDCl_3, 75 MHz): δ = 146.1, 129.1 (2C), 122.3, 114.2 (2C), 81.5, 70.3,
42.4, 19.0; GC-MS (EI, 70 eV): m/z = 179 (M^+, 16), 142 (34), 140 (100); HRMS (ESI-TOF) m/z:
[(M + H)^+] cald for C_{16}H_{21}ClN^+: 237.0585; found, 237.0587.

3.2.3. N-(But-3-yn-1-yl)-4-Isopropylaniline 1c

Yield: 1.07 g, 57% based on but-3-yn-1-yl tosylate. Yellow oil. IR (film): ν = 3397
(m, br), 3298 (m, br), 2118 (w), 1618 (s), 1519 (s), 1288 (m), 1259 (m), 1186 (m), 1051 (w),
822 (m) cm$^{-1}; ^{1}H NMR (CDCl_3, 300 MHz): δ = 7.09–7.01 (m, 2 H, aromatic), 6.62–6.54 (m,
2 H, aromatic), 3.81 (s, br, 1H, NH), 3.29 (t, J = 6.7, NCH_2CH_2), 2.80 (heptuplet, 1H, J = 6.9,
CH_3CHCH_3), 2.48 (td, J = 6.7, 2.6, 2H, NCH_2CH_2), 2.02 (t, J = 2.6, 1H, ≡CH), 1.20 (d, J = 6.9,
6H, (CH_3)_2CH); ^{13}C[^1]H_3NMR (CDCl_3, 75 MHz): δ = 145.6, 138.4, 127.2 (2C), 113.2 (2C),
81.9, 77.2, 70.0, 42.8, 33.1, 24.2, 19.2; GC-MS (EI, 70 eV): m/z = 187 (M^+, 18), 148 (100);
HRMS (ESI-TOF) m/z: [(M + H)^+] cald for C_{18}H_{22}N^+: 282.1444; found, 282.1444.

3.2.4. N-(But-3-yn-1-yl)-4-(tert-Butyl)aniline 1d

Yield: 1.13 g, 56% based on but-3-yn-1-yl tosylate. Yellow oil. IR (film): ν = 3402 (w,
br), 3294 (m, br), 2118 (wv), 1616 (m), 1520 (s), 1261 (m), 1192 (m), 822 (m) cm$^{-1}; ^{1}H NMR
(CDCl_3, 300 MHz): δ = 7.26–7.16 (m, 2 H, aromatic), 6.63–6.53 (d, J = 8.6, 2 H, aromatic),
3.83 (s, br, 1H, NH), 3.28 (t, J = 6.5, 2 H, NCH_2CH_2), 2.46 (td, J = 6.5, 2.5, 2 H, NCH_2CH_2),
2.01 (t, J = 2.5, 1 H, ≡CH), 1.27(s, 9H, t-Bu); ^{13}C[^1]H_3NMR (CDCl_3, 75 MHz): δ = 145.2, 140.6,
126.0 (2C), 112.9 (2C), 81.9, 70.0, 42.7, 33.8, 31.5 (3C), 19.2; GC-MS (EI, 70 eV): m/z = 201
(M^+, 20), 186 (22), 162 (100), 147 (29); HRMS (ESI-TOF) m/z: [(M + H)^+] cald for C_{18}H_{22}N^+: 202.1590; found, 202.1599.

3.2.5. 3-Bromo-N-(but-3-yn-1-yl)-5-Methylaniline 1e

Yield: 998.0 mg, 42% based on but-3-yn-1-yl tosylate. Yellow oil. IR (film): ν = 3394
(w, br), 3299 (m), 2119 (wv), 1517 (s), 1316 (m), 1100 (w), 1037 (w), 803 (m) cm$^{-1}; ^{1}H NMR
(CDCl_3, 300 MHz): δ = 7.29–7.24 (m, 1 H, aromatic), 7.01–6.94 (m, 1 H, aromatic), 6.55 (d,
J = 8.2, 1 H, aromatic), 4.45 (s, br, 1H, NH), 3.34 (q, J = 6.6, NCH_2CH_2), 2.51 (td, J = 6.6,
2.6, 2H, NCH_2CH_2), 2.22 (s, 3H, Me), 2.06 (t, J = 2.6, 1 H, ≡CH); ^{13}C[^1]H_3NMR (CDCl_3,
75 MHz): δ = 142.1, 132.9, 129.0, 127.8, 111.4, 110.0, 81.4, 70.3, 42.6, 20.0, 19.0; GC-MS (EI,
70 eV): m/z = 239 [(M+2)^+, 20], 237 (M^+, 21), 200 (96), 198 (100), 119 (45); HRMS (ESI-TOF)
m/z: [(M + H)^+] cald for C_{14}H_{20}BrN^+: 238.0226; found, 238.0235.

3.2.6. N-(Pent-4-yn-2-yl)aniline 1f

Yield: 891.7 mg, 56% based on pent-4-yn-2-yl tosylate. Yellow oil. IR (film): ν = 3403
(m, 3294 (m), 2116 (w), 1603 (s), 1506 (s), 1316 (s), 1255 (w), 1154 (w), 750 (s) cm$^{-1}; ^{1}H NMR
(CDCl_3, 300 MHz): δ = 7.22–7.12 (m, 2 H, aromatic), 6.75–6.66 (m, 1 H, aromatic), 6.64–6.55
(m, 2 H, aromatic), 3.77–3.61 (m, 2 H, NH+CH_2CH_3), 2.53–2.31 (m, 2H, CH_2CeCl), 2.03 (t,
J = 2.6, 1H, ≡CH), 1.31 (d, J = 6.4, 3H, Me); ^{13}C[^1]H_3NMR (CDCl_3, 75 MHz): δ = 146.8,
129.4 (2C), 117.6, 113.6 (2C), 80.9, 70.7, 47.0, 25.5, 20.0; GC-MS (EI, 70 eV): m/z = 159 (M^+, 13),
120 (100); HRMS (ESI-TOF) m/z: [(M + H)^+] cald for C_{11}H_{13}BrN^+: 160.1121; found, 160.1131.
3.2.7. N-(Hex-5-yn-3-yl)aniline 1g

Yield: 762.3 mg, 44% based on hex-5-yn-3-yl tosylate. Yellow oil. IR (film): ν = 3399 (m), 3294 (m), 2114 (w), 1601 (s), 1504 (s), 1281 (m), 1153 (w), 748 (m) cm\(^{-1}\); 1H NMR (CDCl\(_3\), 300 MHz): δ = 7.23–7.09 (m, 2 H, aromatic), 6.75–6.65 (m, 1 H), 6.65–6.55 (m, 2 H, aromatic), 3.69 (s, br, NH), 3.52–3.33 (m, 1H, CH\(_2\)CH\(_3\)), 2.51–2.36 (m, 2H, NCH\(_2\)CH\(_2\)), 2.00 (t, J = 6.6, 1H, NH), 1.84–1.52 (m, 2 H, CH\(_2\)CH\(_3\)), 0.99 (t, 3H, CH\(_3\)); 13C\(^{1}H\) NMR (CDCl\(_3\), 75 MHz): δ = 147.2, 129.4 (2C), 117.5, 113.5 (2C), 80.9, 70.5, 52.8, 26.8, 23.2, 10.7; GC-MS (EI, 70 eV): m/z = 173 (M\(^{+}\), 11), 134 (100); HRMS (ESI-TOF) m/z: [(M + H\(^{+}\))]\(^{+}\) cald for C\(_{12}\)H\(_{16}\)N\(^{+}\): 174.1277; found, 174.1300.

3.2.8. N-Benzylbut-3-yn-1-amine 1i

Yield: 1.2 g, 75% based on but-3-yn-1-yl tosylate. Yellow oil. IR (film): ν = 3296 (s), 2915 (m), 2836 (m), 2116 (w), 1454 (m), 1120 (m), 738 (s), 699 (m), 640 (s) cm\(^{-1}\); 1H NMR (CDCl\(_3\), 300 MHz): δ = 7.35–7.10 (m, 5H, Ph), 3.80 (q, J = 6.6, 1H, CH\(_3\)), 2.72–2.53 (m, 2H, NCH\(_2\)CH\(_3\)), 2.40–2.27 (m, 2 H, NCH\(_2\)CH\(_2\)), 1.98 (s, br, 1 H, NH), 1.36 (d, J = 6.6, 3H, Me); 13C\(^{1}H\) NMR (CDCl\(_3\), 75 MHz): δ = 140.1, 128.4 (2C), 128.1 (2C), 127.0, 82.6, 69.5, 53.4, 47.3, 19.5; GC-MS (EI, 70 eV): m/z = 159 (M\(^{+}\), 1), 120 (58), 91 (100). HRMS (ESI-TOF) m/z: [(M + H\(^{+}\))]\(^{+}\) cald for C\(_{11}\)H\(_{14}\)N\(^{+}\): 160.1121; found, 160.1130. The spectroscopic data agreed with those reported [19].

3.2.9. N-(1-Phenylethyl)but-3-yn-1-amine 1m

Yield: 1.1 g, 63% based on but-3-yn-1-yl tosylate. Yellow oil. IR (film): 3302 (s), 2968 (s), 2927 (m), 2117 (w), 1452 (m), 1130 (m), 762 (m), 701 (s) cm\(^{-1}\); 1H NMR (CDCl\(_3\), 300 MHz): δ = 7.35–7.10 (m, 5H, Ph), 3.80 (q, J = 6.6, 1H, CH\(_3\)), 2.72–2.53 (m, 2H, NCH\(_2\)CH\(_3\)), 2.40–2.27 (m, 2 H, NCH\(_2\)CH\(_2\)), 1.98 (s, br, 1 H, NH), 1.36 (d, J = 6.6, 3H, Me); 13C\(^{1}H\) NMR (CDCl\(_3\), 75 MHz): δ = 140.1, 128.4 (2C), 128.1 (2C), 127.0, 82.6, 69.5, 53.4, 47.3, 19.5; GC-MS (EI, 70 eV): m/z = 159 (M\(^{+}\), 1), 120 (58), 91 (100). HRMS (ESI-TOF) m/z: [(M + H\(^{+}\))]\(^{+}\) cald for C\(_{11}\)H\(_{14}\)N\(^{+}\): 160.1121; found, 160.1130. The spectroscopic data agreed with those reported [20].

3.2.10. N-tert-Butylbut-3-yn-1-amine 1n

Yield: 689 mg, 55% based on but-3-yn-1-yl tosylate. Colorless oil. IR (film): ν = 3310 (m), 2967 (s), 2866 (s), 2118 (w), 1450 (m), 1365 (m), 1060 (w), 633 (m) cm\(^{-1}\); 1H NMR (CDCl\(_3\), 300 MHz): δ = 2.73 (t, J = 6.7, 2H, NCH\(_2\)), 2.37 (td, J = 6.7, 2.6, 2H, CH\(_2\)C\(_{2}\)), 2.06–1.97 (m, 2 H, NH + CH + NH), 1.12 (s, 9H, t-Bu); 13C\(^{1}H\) NMR (CDCl\(_3\), 75 MHz): δ = 82.7, 69.4, 50.3, 41.2, 29.0 (3C), 20.5; HRMS (ESI-TOF) m/z: [(M + H\(^{+}\))]\(^{+}\) cald for C\(_{8}\)H\(_{16}\)N\(^{+}\): 126.1277; found, 126.1288. The spectroscopic data agreed with those reported [21].

3.3. Preparation of Substrates 1h–k

N-Substituted but-3-yn-1-amines 1h–k were prepared by propargylation of the corresponding imines as described below. All starting materials were commercially available (Merck Life Science s.r.l., Milano, Italy) and were used without further purification.

N-Benzylidenearanine, N-(4-bromobenzylidene)aniline, N-(4-methoxybenzylidene)aniline, 4-chloro-N-(4-methoxybenzylidene)aniline were prepared by mixing the corresponding aldehydes (10 mmol; benzaldehyde, 1.05 g; 4-bromobenzaldehyde, 1.85 g; 4-methoxybenzaldehyde, 1.35 g) with anilines (10 mmol; aniline, 925 mg; 4-chloroaniline, 1.28 g) and Na\(_2\)SO\(_4\) (5 g) in toluene (40 mL). The mixture was refluxed for 24 h. Solvent was removed in vacuo to afford the crude imine which was used directly in the next step. Zinc powder (2 g, 30 mmol) was washed with 2 N HCl (5 mL), H\(_2\)O (until neutral), MeOH (25 mL), and tetrahydrofuran (THF) (25 mL) in this sequence, before being suspended in anhydrous THF (25 mL) under nitrogen. A THF solution (75 mL) of the crude imine (obtained as above) was added, followed by 3-bromopropyne (30 mmol, 3.5 g; 4.4 mL of an 80 wt % solution in toluene), which was added dropwise at 0 °C followed by stirring for 30 min. The mixture was allowed to warm up to room temperature and stirred for additional 24 h. Water (100 mL) and Et\(_2\)O (100 mL) were added, and the reaction mixture was filtered through Celite.
The aqueous phase was extracted with AcOEt (3 × 100 mL) and the combined organic layers were washed with brine (100 mL), dried over K₂CO₃, and concentrated under vacuum. The crude products were purified by column chromatography on silica gel using as eluent hexane–AcOEt from 100:0 to 95:5.

3.3.1. N-(1-Phenylbut-3-yn-1-yl)aniline 1h

Yield: 1.16 g, 52% based on starting N-benzylideneaniline. Yellow solid, mp 67.2–68.2. IR (KBr): ν = 3410 (m), 3256 (m), 2114 (w), 1605 (s), 1512 (s), 1327 (m), 1265 (w), 756 (s) cm⁻¹; ¹H NMR (CDCl₃, 300 MHz): δ = 7.45–7.20 (m, 5 H, aromatic), 7.16–7.04 (m, 2H, aromatic), 6.72–6.63 (m, 1H, aromatic), 6.60–6.49 (m, 2H, aromatic), 4.54 (t, J = 6.0, 1H, CH₂Ph), 4.41 (s, 1H, NH), 2.85–2.56 (m, 2H, CH₂C=C), 2.06 (t, J = 2.6, 1H, ≡CH); ¹³C[¹H] NMR (CDCl₃, 75 MHz): δ = 147.0, 142.0, 129.1 (2C), 128.7 (2C), 127.5, 126.4 (2C), 117.8, 113.7 (2C), 80.3, 71.4, 56.4, 28.1; GC-MS (EI, 70 eV): m/z = 221 (M⁺, 7), 182 (100), 104 (45); HRMS (ESI-TOF) m/z: [(M + H)⁺] cald for C₁₆H₁₆N⁺: 222.1277; found, 222.1298. The spectroscopic data agreed with those reported [22].

3.3.2. N-(1-(4-Bromobenzylidene)but-3-yn-1-yl)aniline 1i

Yield: 1.59 g, 53% based on starting N-(4-bromobenzylidene)aniline. Yellow oil. IR (film): ν = 3402 (w), 3294 (m), 3048 (w), 2114 (w), 1605 (s), 1505 (s), 1427 (w), 1312 (m), 1265 (m), 1072 (m), 1011 (m), 818 (m), 748 (s), 694 (m), 648 (m, br) cm⁻¹; ¹H NMR (CDCl₃, 300 MHz): δ = 7.45 (distorted d, J = 8.3, 2H, aromatic), 7.28 (distorted d, J = 8.3, 2H, aromatic), 7.17–7.05 (m, 2H, aromatic), 6.74–6.64 (m, 1H, aromatic), 6.56–6.45 (m, 2H, aromatic), 4.48 (s, br, 1H, NH or CH₂Ph), 4.39 (s, br, 1H, CH₂Ph or NH), 2.82–2.55 (m, 2H, CH₂C=C≡), 2.08 (t, J = 2.5, 1H, ≡CH); ¹³C[¹H] NMR (CDCl₃, 75 MHz): δ = 146.6, 141.1, 131.8 (2C), 129.2 (2C), 128.2 (2C), 121.3, 118.1, 113.7 (2C), 79.8, 71.8, 55.8, 28.0; GC-MS (EI, 70 eV): m/z = 301 [(M + 2)⁺, 9], 299 (M⁺, 10), 262 (96), 260 (100), 104 (57); HRMS (ESI-TOF) m/z: [(M + H)⁺] cald for C₁₉H₁₅BrN⁺: 300.0382; found, 300.0420.

3.3.3. N-(1-(4-Bromobenzylidene)but-3-yn-1-yl)aniline 1j

Yield: 1.45 g, 57% based on starting N-(4-methoxybenzylidene)aniline. Yellow oil. IR (film): ν = 3402 (m), 3287 (m), 2118 (wv), 1605 (s), 1505 (s), 1173 (m), 1099 (wv), 1034 (w), 752 (m) cm⁻¹; ¹H NMR (CDCl₃, 300 MHz): δ = 7.30 (distorted d, J = 8.3, 2H, aromatic), 7.15–7.04 (m, 2H, aromatic), 6.85 (distorted d, J = 8.3, 2H, aromatic), 6.71–6.62 (m, 1H, aromatic), 6.57–6.50 (m, 2H, aromatic), 4.48 (t, J = 6.0, 1H, CH₂Ph), 4.35 (s, br, 1H, NH), 3.75 (s, 3H, OMe), 2.80–2.52 (m, 2H, CH₂C≡), 2.05 (s, br, 1H, ≡CH); ¹³C[¹H] NMR (CDCl₃, 75 MHz): δ = 158.9, 147.0, 134.1, 129.1 (2C), 127.4 (2C), 117.7, 114.0 (2C), 113.7 (2C), 80.5, 71.3, 55.8, 55.2, 28.1; GC-MS (EI, 70 eV): m/z = 251 (M⁺, 9), 212 (100); HRMS (ESI-TOF) m/z: [(M + H)⁺] cald for C₁₉H₁₈NO⁺: 252.1383; found, 252.1423.

3.3.4. 4-Chloro-N-(1-(4-Methoxyphenyl)but-3-yn-1-yl)aniline 1k

Yield: 1.69 g, 59% based on starting 4-chloro-N-(4-methoxybenzylidene)aniline. Yellow oil. IR (film): ν = 3410 (m), 3294 (m), 2114 (wv), 1605 (s), 1504 (s), 1250 (s), 1173 (m), 1088 (w), 1034 (m), 818 (m) cm⁻¹; ¹H NMR (CDCl₃, 300 MHz): δ = 7.32–7.20 (m, 2H, aromatic), 7.07–6.97 (m, 2H, aromatic), 6.90–6.80 (m, 2H, aromatic), 6.50–6.40 (m, 2H, aromatic), 4.50–4.30 (m, 2H, CH₂Ph + NH), 3.76 (s, 3H, OMe), 2.80–2.50 (m, 2H, CH₂C≡), 2.07 (t, J = 2.5, 1H, ≡CH); ¹³C[¹H] NMR (CDCl₃, 75 MHz): δ = 159.0, 145.6, 133.5, 128.9 (2C), 127.4 (2C), 122.3, 114.8 (2C), 114.1 (2C), 80.2, 71.5, 55.9, 55.2, 28.1; GC-MS (EI, 70 eV): m/z = 285 (M⁺, 9), 245 (100); HRMS (ESI-TOF) m/z: [(M + H)⁺] cald for C₁₇H₁₇ClNO⁺: 286.0993; found, 286.0999.

3.4. General Procedure for the Palladium-Catalyzed Oxidative Carbonylation of N-Substituted 3-yn-1-Amines 1a–n in MeOH

A 40 mL stainless steel autoclave was charged in the presence of air with PdI₂ (9.0 mg, 2.5 × 10⁻² mmol), KI (41.5 mg, 2.5 × 10⁻¹ mmol) and a solution of 1 (0.5 mmol; 1a, 72.6 mg;
3.4.1. (Z)-Methyl 2-(2-Oxo-1-Phenylpyrrolidin-3-ylidene)acetate 2a

Yield: 98.3 mg, starting from 72.6 mg of 1a (85%) (Table 2, entry 1). White solid, mp 102-103 °C. IR (KBr): ν = 1733 (s), 1696 (s), 1496 (m), 1398 (m), 1307 (m), 1238 (m), 762 (m cm⁻¹). 1H NMR (CDCl₃, 300 MHz): δ = 7.72–7.62 (m, 2H, aromatic), 7.42–7.31 (m, 2H, aromatic), 7.21–7.12 (m, 1H, aromatic), 6.17 (t, J = 2.4, 1H, =CH), 3.87 (t, J = 6.6, 2H, NCH₂), 3.85 (s, 3H, CO₂Me), 2.92 (td, J = 6.6, 2.4, 2H, NCH₂CH₂); 13C¹[H] NMR (CDCl₃, 75 MHz): δ = 167.3, 164.4, 139.0, 138.6, 128.9 (2C), 125.2, 122.7, 119.8 (2C), 52.3, 45.3, 24.2; HRMS (ESI-TOF) m/z: [(M + H)⁺] cald for C₁₃H₁₁NO₃⁺: 232.0968; found, 232.0978.

3.4.2. (Z)-Methyl 2-(1-(4-Chlorophenyl)-2-Oxopyrrolidin-3-Ylidene)acetate 2b

Yield: 102.3 mg, starting from 89.8 mg of 1b (77%) (Table 2, entry 8). White solid, mp 95–96 °C. IR (KBr): ν = 1733 (s), 1696 (s), 1496 (m), 1394 (m), 1241 (m), 1085 (w), 1010 (w), 892 (w), 828 (m cm⁻¹). 1H NMR (CDCl₃, 300 MHz): δ = 7.68–7.60 (m, 2H, aromatic), 7.36–7.28 (m, 2H, aromatic), 6.19 (s, br, 1H, =CH), 3.91–3.78 (m, 2H, NCH₂), 3.85 (s, 3H, CO₂Me), 2.93 (td, J = 7.1, 2.3, 2H, NCH₂CH₂); 13C¹[H] NMR (CDCl₃, 75 MHz): δ = 167.1, 164.4, 138.2, 137.6, 130.3, 128.9 (2C), 123.1, 120.8 (2C), 52.3, 45.2, 24.0; HRMS (ESI-TOF) m/z: [(M + H)⁺] cald for C₁₃H₁₃ClNO₃⁺: 266.0578; found, 266.0550.

3.4.3. (Z)-Methyl 2-(1-(4-Isopropylphenyl)-2-Oxopyrrolidin-3-Ylidene)acetate 2c

Yield: 101.1 mg, starting from 93.6 mg of 1c (74%) (Table 2, entry 10). Yellow solid, mp 94–95 °C. IR (KBr): ν = 1734 (s), 1696 (s), 1516 (m), 1398 (m), 1307 (w), 1239 (m), 1017 (m), 835 (m cm⁻¹). 1H NMR (CDCl₃, 300 MHz): δ = 7.62–7.53 (m, 2H, 2H, aromatic), 7.26–7.18 (m, 2H, N aromatic), 6.16 (t, J = 2.3, 1H, =CH), 3.86 (t, J = 6.4, 2H, NCH₂), 3.85 (s, 3H, CO₂Me), 2.97–2.83 (m, 3H, NCH₂CH₂ + CH₂Me₂), 1.22 (d, J = 7.0, 6H, CH₃(CH₂)₂); 13C¹[H] NMR (CDCl₃, 75 MHz): δ = 167.4, 164.3, 146.0, 138.7, 136.7, 126.8 (2C), 122.4, 119.9 (2C), 52.3, 45.4, 33.6, 24.1, 23.9 (2C); HRMS (ESI-TOF) m/z: [(M + H)⁺] cald for C₁₇H₂₃NO₃⁺: 274.1438; found, 274.1434.

3.4.4. (Z)-Methyl 2-(1-(4-(tert-Butyl)phenyl)-2-Oxopyrrolidin-3-Ylidene)acetate 2d

Yield: 100.6 mg, starting from 100.7 mg of 1d (70%) (Table 2, entry 12). Yellow solid, mp 96–97 °C. IR (KBr): ν = 1736 (s), 1690 (s), 1520 (m), 1396 (m), 1234 (m), 1080 (w), 1049 (m), 895 (m), 833 (s cm⁻¹). 1H NMR (CDCl₃, 300 MHz): δ = 7.68–7.50 (m, 2H, aromatic), 7.43–7.30 (m, 2H, aromatic), 6.15 (s, br, 1H, =CH), 3.92–3.75 (m, 2H, NCH₂), 3.84 (s, 3H, CO₂Me), 2.95–2.82 (m, 2H, NCH₂CH₂), 1.30 (s, 9H, t-Bu); 13C¹[H] NMR (CDCl₃, 75 MHz): δ = 167.3, 164.3, 148.2, 138.8, 136.4, 125.7 (2C), 122.4, 119.6 (2C), 52.3, 45.3, 34.4, 31.3 (3C), 24.2; HRMS (ESI-TOF) m/z: [(M + H)⁺] cald for C₁₇H₂₅NO₃⁺: 288.1594; found, 288.1589.

3.4.5. (Z)-Methyl 2-(1-(3-Bromo-5-Methylphenyl)-2-Oxopyrrolidin-3-Ylidene)acetate 2e

Yield: 126.4 mg, starting from 119.1 mg of 1e (78%) (Table 2, entry 13). Yellow solid, mp 89–90 °C. IR (KBr): ν = 1733 (s), 1699 (s), 1496 (m), 1411 (w), 1016 (w) cm⁻¹. 1H NMR (CDCl₃, 300 MHz): δ = 7.47 (s, 1H, aromatic), 7.22–7.11 (m, 2H, aromatic), 6.20 (t, J = 2.2, 1H, =CH), 3.87–3.75 (m, 2H, NCH₂), 3.81 (s, 3H, CO₂Me), 3.00 (td, J = 6.5, 2.4, 2H, NCH₂CH₂), 2.43 (s, 3H, CH₃); 13C¹[H] NMR (CDCl₃, 75 MHz): δ = 167.2, 165.0, 140.3, 137.7,
3.4.6. (Z)-Methyl 2-(5-Methyl-2-Oxo-Phenylpyrroolidin-3-Ylidene)acetate 2f

Yield: 94.4 mg, starting from 79.6 mg of 1f (77%) (Table 2, entry 15). Yellow solid, mp 36–37 °C. IR (KBr): ν = 1733 (s), 1705 (s), 1596 (m), 1469 (m), 1388 (s), 1239 (m), 1015 (w) cm⁻¹; 1H NMR (CDCl₃, 300 MHz): δ = 7.47–7.33 (m, 4H, aromatic), 7.25–7.16 (m, 1H, aromatic), 6.16 (t, J = 2.4, 1H, =CH), 4.43–4.28 (m, 1H, NCHMe), 3.82 (s, 3H, CO₂Me), 3.14 (ddd, J = 17.3, 7.7, 2.4, 1H, NCHMeCH₂), 2.50 (ddd, J = 17.5, 4.3, 2.4, 1H, NCH(NMe)CH₂), 1.23 (d, J = 6.2, 2H, CH₃), 13C¹H NMR (CDCl₃, 75 MHz): δ = 167.4, 164.3, 138.1, 136.9, 129.0 (2C), 126.1, 123.5 (2C), 122.7, 52.4, 52.3, 33.1, 20.8; HRMS (ESI-TOF) m/z: [(M + H)+] cald for C₁₄H₁₅BrNO₃$: 324.0220; found, 324.0212.

3.4.7. (Z)-Methyl 2-(5-Ethyl-2-Oxo-Phenylpyrroolidin-3-Ylidene)acetate 2g

Yield: 101.1 mg, starting from 86.6 mg of 1g (78%) (Table 2, entry 16). Yellow solid, mp 39–40 °C. IR (KBr): ν = 1733 (s), 1671 (s), 1496 (m), 1394 (m), 1240 (m), 1016 (w) cm⁻¹; 1H NMR (CDCl₃, 300 MHz): δ = 7.47–7.33 (m, 4H, aromatic), 7.25–7.16 (m, 1H, aromatic), 6.17 (t, J = 2.3, 1H, =CH), 4.31–4.19 (m, 1H, NCH(NMe)CH₂), 3.82 (s, 3H, CO₂Me), 3.05 (ddd, J = 17.6, 7.9, 2.3, 1H, NCH(NMe)CH₂), 2.66–2.53 (m, 1H, NCH(NMe)CH₂), 1.81–1.63 (m, 1H, CH(NMe)CH₂), 1.52–1.34 (m, 1H, CH(NMe)CH₂), 0.83 (t, J = 7.4, 3H, CH₂CH₃); 13C¹H NMR (CDCl₃, 75 MHz): δ = 167.4, 164.5, 138.2, 137.0, 129.0 (2C), 126.2, 123.5 (2C), 122.6, 57.3, 52.3, 29.9, 26.2, 8.2; HRMS (ESI-TOF) m/z: [(M + H)+] cald for C₁₃H₁₃NO₃$: 260.1281; found, 260.1309.

3.4.8. (Z)-Methyl 2-(2-Oxo-1,5-Diphenylpyrroloidin-3-Ylidene)acetate 2h

Yield: 126.0 mg, starting from 110.7 mg of 1h (82%) (Table 2, entry 17). White solid, mp 157–158 °C. IR (KBr): ν = 1732 (s), 1697 (s), 1597 (w), 1492 (m), 1385 (m), 1242 (m), 1011 (m) cm⁻¹; 1H NMR (CDCl₃, 300 MHz): δ = 7.48–7.40 (m, 2H, aromatic), 7.33–7.16 (m, 7H, aromatic), 7.10–7.02 (m, 1H, aromatic), 6.17 (t, J = 2.3, 1H, =CH), 5.27 (dd, J = 8.3, 3.6, 1H, CHPh), 3.86 (s, 3H, CO₂Me), 3.39 (ddd, J = 17.2, 8.3, 2.3, 1H, NCHPhCH₂), 2.73 (ddd, J = 17.2, 3.6, 2.3, 1H, NCHPhCH₂); 13C¹H NMR (CDCl₃, 75 MHz): δ = 167.1, 165.0, 140.8, 137.6, 137.5, 129.1 (2C), 128.7 (2C), 128.1, 125.9 (2C), 125.6, 123.2, 122.3 (2C), 60.7, 53.4, 35.6; HRMS (ESI-TOF) m/z: [(M + H)+] cald for C₁₉H₁₉NO₃$: 308.1281; found, 308.1286.

3.4.9. (Z)-Methyl 2-(5-(4-Bromophenyl)-2-Oxo-Phenylpyrroloidin-3-Ylidene)acetate 2i

Yield: 135.2 mg, starting from 150.1 mg of 1i (70%) (Table 2, entry 18). White solid, mp 151–152 °C. IR (KBr): ν = 1736 (s), 1697 (s), 1612 (w), 1489 (m), 1389 (m), 1250 (s), 1180 (w), 1026 (w), 833 (m) cm⁻¹; 1H NMR (CDCl₃, 300 MHz): δ = 7.45–7.35 (m, 4H, aromatic), 7.28–7.19 (m, 2H, aromatic), 7.13–7.04 (m, 3H, aromatic), 6.19 (t, J = 2.3, 1H, =CH), 5.25 (ddd, J = 8.3, 3.8, 1H, CHAr), 3.86 (s, 3H, CO₂Me), 3.39 (ddd, J = 17.2, 8.3, 2.3, 1H, CHHC), 2.69 (ddd, J = 17.2, 3.8, 2.3, 1H, CHHC); 13C¹H NMR (CDCl₃, 75 MHz): δ = 167.0, 164.9, 139.8, 137.3, 137.0, 132.3 (2C), 128.8 (2C), 127.7 (2C), 125.8, 123.5, 122.3 (2C), 122.0, 60.1, 52.4, 35.4; HRMS (ESI-TOF) m/z: [(M + H)+] cald for C₁₉H₁₇BrNO₃$: 386.0386; found, 386.0384.

3.4.10. (Z)-Methyl 2-(5-(4-Methoxyphenyl)-2-Oxo-Phenylpyrroloidin-3-Ylidene)acetate 2j

Yield: 119.8 mg, starting from 125.7 mg of 1j (71%) (Table 2, entry 19). White solid, mp 95–96 °C. IR (KBr): ν = 1721 (s), 1694 (s), 1597 (m), 1512 (w), 1472 (w), 1373 (m), 1103 (m), 1034 (m), 1003 (m), 895 (m), 841 (m), 772 (m) cm⁻¹; 1H NMR (CDCl₃, 300 MHz): δ = 7.50–7.34 (m, 2H, aromatic), 7.31–7.16 (m, 2H, aromatic), 7.16–6.99 (m, 3H, aromatic), 6.88–6.71 (m, 2H, aromatic), 6.17 (s, br, 1H, =CH), 5.22 (ddd, J = 7.8, 3.6, 1H, CHAr), 3.86 (s, 3H, CO₂Me), 3.73 (s, 3H, OMe), 3.44–3.25 (m, 1H, CHHC), 2.81–2.60 (m, 1H, CHHC); 13C¹H NMR (CDCl₃, 75 MHz): δ = 167.2, 164.9, 159.3, 157.7, 137.6, 132.6, 128.7 (2C), 127.2 (2C), 125.6, 123.0, 122.6 (2C), 114.4 (2C), 60.3, 55.2, 52.3, 35.8; HRMS (ESI-TOF) m/z: [(M + H)+] cald for C₂₀H₁₉NO₄$: 338.1387; found, 338.1381.
3.4.11. (Z)-Methyl 2-(1-(4-Chlorophenyl)-5-(4-Methoxyphenyl)-2-Oxopyrrolidin-3-Ylidene)acetate 2k

Yield: 130.1 mg, starting from 142.9 mg of 1k (70%) (Table 2, entry 20). Yellow solid, mp 119-120 °C. IR (KBr): ν = 1736 (s), 1695 (w), 1511 (m), 1690 (m), 1389 (m), 1249 (s), 1180 (m), 1011 (m), 883 (m) cm⁻¹; ¹H NMR (CDCl₃, 300 MHz): δ = 7.43–7.34 (m, 2H, aromatic), 7.25–7.15 (m, 2H, aromatic), 7.15–7.05 (m, 2H, aromatic), 6.87–6.76 (m, 2H, aromatic). HRMS (ESI-TOF) m/z: 1249 (s), 1180 (m), 1011 (m), 895 (w), 833 (m) cm⁻¹.

3.4.12. (Z)-Methyl 2-(1-Benzyl-2-Oxopyrrolidin-3-Ylidene)acetate 2l

Yield: 97.2 mg, starting from 86.6 mg of 1l (75%) (Table 2, entry 26). Yellow oil. IR (film): ν = 1736 (s), 1697 (w), 1438 (m), 1338 (w), 1235 (m), 1146 (2C), 1060, 55.3, 52.4, 35.7; HRMS (ESI-TOF) m/z: [(M + H)+] calcd for C₂₀H₁₉ClNO₄⁺: 372.0997; found, 372.0995.

3.4.13. (Z)-Methyl 2-(2-Oxo-1-(1-Phenylethyl)pyrrolidin-3-Ylidene)acetate 2m

Yield: 119.7 mg, starting from 86.6 mg of 1m (75%) (Table 2, entry 26). Yellow oil. IR (film): ν = 1733 (s), 1674 (s), 1512 (m), 1417 (m), 1235 (m), 1017 (w) cm⁻¹; ¹H NMR (CDCl₃, 300 MHz): δ = 7.43–7.15 (m, 5H, Ph), 6.11 (t, J = 2.4, 1H, =CH), 4.51 (s, 2H, CH₂Ph), 3.86 (s, 3H, CO₂Me), 3.29 (t, J = 6.5, 2H, NCH₂), 2.76 (td, J = 6.5, 2.4, 2H, NCH₂CH₂); ¹³C[¹H] NMR (CDCl₃, 75 MHz): δ = 167.4, 165.2, 138.4, 135.7, 128.8 (2C), 128.4 (2C), 127.8, 121.8, 52.2, 47.2, 43.5, 24.2; HRMS (ESI-TOF) m/z: [(M + H)+] calcd for C₁₄H₁₆NO₃⁺: 246.1128; found, 246.1128.

3.4.14. (Z)-Methyl 2-(1-tert-Butyl)-2-Oxopyrrolidin-3-Ylidene)acetate 2n

Yield: 100.6 mg, starting from 72.5 mg of 1a (82%) (Table 2, entry 4). White solid, mp 61–62 °C. IR (KBr): ν = 1728 (s), 1690 (s), 1598 (w), 1496 (m), 1398 (m), 1306 (m), 1234 (m), 1095 (w), 1030 (m), 761 (cm⁻¹); ¹H NMR (CDCl₃, 300 MHz): δ = 7.70–7.63 (m, 2H, aromatic), 7.40–7.30 (m, 2H, aromatic), 7.20–7.11 (m, 1H, aromatic), 6.16 (t, J = 2.3, 1H, =CH), 2.3, 1H, =CH), 3.84 (s, 3H, OMe), 3.37 (ddd, J = 17.1, 8.0, 2.3, 1H, CHH=), 2.73 (ddd, J = 17.1, 3.6, 2.3, 1H, CHH=); ¹³C[¹H] NMR (CDCl₃, 75 MHz): δ = 173.6, 1695 (s), 1613 (w), 1511 (m), 1690 (m), 1389 (m), 702 (m) cm⁻¹.

3.5. General Procedure for the Palladium-Catalyzed Oxidative Carbonylation of N-Substituted 3-yn-1-Amines 1a and 1f in Different Alcoholic Solvents

A 40 mL stainless steel autoclave was charged in the presence of air with PdI₂ (9.0 mg, 2.5 × 10⁻² mmol), KI (41.5 mg, 2.5 × 10⁻² mmol) and a solution of 1 (0.5 mmol; 1a, 72.6 mg; 1f, 79.6 mg) in EtOH or isoPrOH (5 mL) or tert-ButOH (12.5 mL only for 1a). The autoclave was sealed and, while the mixture was stirred, the autoclave was pressurized with CO (32 atm) and air (up to 40 atm). After being stirred at 100 °C for the required time (2 h for 1a and 5h for 1f) the autoclave was cooled, degassed and opened. The solvent was evaporated and the products were purified by column chromatography on silica gel using as eluent hexane/AcOEt 7:3 for 2a′, 2a″ and 2a‴; hexane/AcOEt 6:4 for 2f and 2f‴.

3.5.1. (Z)-Ethyl 2-(2-Oxo-1-Phenylpyrrolidin-3-Ylidene)acetate 2a′

Yield: 100.6 mg, starting from 72.5 mg of 1a (82%) (Table 2, entry 4). White solid, mp 61–62 °C. IR (KBr): ν = 1728 (s), 1690 (s), 1598 (w), 1496 (m), 1398 (m), 1306 (m), 1234 (m), 1095 (w), 1030 (m), 761 (cm⁻¹); ¹H NMR (CDCl₃, 300 MHz): δ = 7.70–7.63 (m, 2H, aromatic), 7.40–7.30 (m, 2H, aromatic), 7.20–7.11 (m, 1H, aromatic), 6.16 (t, J = 2.3, 1H, =CH).
3.5.2. (Z)-Isopropyl 2-(2-Oxo-1-phenylpyrrolidin-3-Ylidene)acetate 2a"

Yield: 93.4 mg, starting from 72.7 mg of 1a (72%) (Table 2, entry 5). White solid, mp 85–86 °C. IR (KBr): ν = 1723 (s), 1699 (s), 1598 (w), 1496 (m), 1398 (m), 1306 (m), 1241 (m), 1106 (m), 970 (w), 762 (m) cm⁻¹; 1H NMR (CDCl₃, 300 MHz): δ = 7.66 (dist d, J = 8.0, 2H, aromatic), 7.34 (t, J = 7.6, 2H, aromatic), 7.14 (dist d, J = 7.1, 1H), 6.14 (s, br, 1H, =CH), 5.22 (quint, J = 6.1, 1H, CHMe₂), 3.82 (t, J = 6.5, 2H, NCH₂), 2.92–2.80 (m, 2H, NCH₂CH₂), 1.34 (d, J = 6.1, 6H, CH(CH₃)₂); 13C[¹H] NMR (CDCl₃, 75 MHz): δ = 166.8, 164.4, 139.2, 137.9, 128.8 (2C), 125.0, 123.4, 119.7 (2C), 68.9, 45.2, 24.1, 21.7 (2C); HRMS (ESI-TOF) m/z: [(M + H⁺)⁺] calcd for C₁₅H₁₈NO₃⁺: 286.1215; found, 286.1213.

3.5.3. (Z)-tert-Butyl 2-(2-Oxo-1-phenylpyrrolidin-3-Ylidene)acetate 2a””

Yield: 73.8 mg, starting from 72.5 mg of 1a (54%) (Table 2, entry 7). Yellow solid, mp 95–96 °C. IR (KBr): ν = 1723 (s), 1699 (s), 1598 (w), 1496 (m), 1300 (m), 1251 (m), 1161 (m), 759 (w) cm⁻¹; 1H NMR (CDCl₃, 300 MHz): δ = 7.67 (dist d, J = 8.1, 2H, aromatic), 7.36 (t, J = 7.7, 2H, aromatic), 7.15 (t, J = 7.2, 1H, aromatic), 6.11 (s, br, 1H, =CH), 3.85 (t, J = 6.4, 2H, NCH₂), 2.92–2.80 (m, 2H, NCH₂CH₂), 1.57 (s, 9H, t-Bu); 13C[¹H] NMR (CDCl₃, 75 MHz): δ = 165.8, 164.5, 139.3, 136.8, 128.9 (2C), 125.0, 124.4, 119.8 (2C), 82.2, 45.3, 28.1 (3C), 24.2; HRMS (ESI-TOF) m/z: [(M + H⁺)⁺] calcd for C₁₅H₁₈NO₃⁺: 274.1438; found, 274.1444.

3.5.4. (Z)-Ethyl 2-(1-Benzyl-2-oxopyrrolidin-3-Ylidene)acetate 2l’

Yield: 60.9 mg, starting from 79.7 mg of 1l (47%) (Table 2, entry 22). Yellow solid, mp 54–55 °C. IR (KBr): ν = 1728 (s), 1690 (s), 1688 (s), 1446 (w), 1337 (w), 1230 (m), 1030 (m) cm⁻¹; 1H NMR (CDCl₃, 300 MHz): δ = 7.38–7.18 (m, 5H, Ph), 6.11 (t, J = 2.4, 1H, =CH), 4.51 (s, 2H, CH₂Ph), 4.34 (q, J = 7.1, 2H, CH₂Ph), 3.29 (t, J = 6.4, 2H, NCH₂), 2.76 (td, J = 6.4, 2.4, 2H, NCH₂CH₂), 1.36 (t, J = 7.1, 3H, CH₃CH₂); 13C[¹H] NMR (CDCl₃, 75 MHz): δ = 166.8, 165.3, 138.1, 135.8, 128.7 (2C), 128.4 (2C), 127.8, 122.2, 61.3, 47.2, 43.5, 24.3, 14.1; HRMS (ESI-TOF) m/z: [(M + H⁺)⁺] calcd for C₁₆H₂₀NO₃⁺: 260.1281; found, 260.1278.

3.5.5. (Z)-Isopropyl 2-(1-Benzyl-2-oxopyrrolidin-3-Ylidene)acetate 2l”

Yield: 65.6 mg, starting from 79.5 mg of 1l (48%) (Table 2, entry 23). Yellow solid, mp 51–52 °C. IR (KBr): ν = 1725 (s), 1696 (s), 1496 (w), 1446 (m), 1238 (s), 1108 (m), 970 (w) cm⁻¹; 1H NMR (CDCl₃, 300 MHz): δ = 7.37–7.20 (m, 5H, Ph), 6.12–6.06 (m, 1H, =CH), 5.22 (heptet, J = 6.3, 1H, CHMe₂), 4.51 (s, 2H, CH₂Ph), 3.27 (t, J = 6.5, 2H, NCH₂), 2.74 (td, J = 6.5, 2.3, 2H, NCH₂CH₂), 1.36 (d, J = 6.3, 6H, CH(CH₃)₂); 13C[¹H] NMR (CDCl₃, 75 MHz): δ = 166.3, 165.2, 137.7, 135.8, 128.7 (2C), 128.4 (2C), 127.8, 122.5, 68.9, 47.2, 43.4, 24.3, 21.8 (2C); HRMS (ESI-TOF) m/z: [(M + H⁺)⁺] calcd for C₁₆H₂₀NO₃⁺: 274.1438; found, 274.1413.

3.6. Palladium-Catalyzed Oxidative Carbonylation of N-(but-3-yn-1-yl)-4-(tert-Butyl)aniline 1d to (Z)-Methyl 2 (1-(4-(tert-Butyl)phenyl)-2-oxopyrrolidin-3-Ylidene)acetate 2d in Larger Scale

A 300 mL stainless steel autoclave was charged in the presence of air with PdI₂ (54.0 mg, 1.5 × 10⁻³ mmol), KI (249.0 mg, 1.5 mmol) and a solution of N-(but-3-yn-1-yl)-4-(tert-butyl)aniline 1d (602.3 mg, 2.99 mmol) in MeOH (30 mL). The autoclave was sealed and, while the mixture was stirred, the autoclave was pressurized with CO (32 atm) and air (up to 40 atm). After being stirred at 100 °C for 2 h, the autoclave was cooled, degassed and opened. The solvent was evaporated and the products were purified by column chromatography on silica gel using eluent hexane/AcOEt 8:2, to give pure (Z)-methyl 2(1-(4-(tert-butyl)phenyl)-2-oxopyrrolidin-3-ylidene)acetate 2d as a yellow solid (Yield: 620.0 mg, 72% based on starting 1d).
4. Conclusions

In conclusion, we have shown that our simple PdI$_2$-KI catalytic system is able to catalyze the oxidative carbonylation of readily available homopropargylic amines 1 to give (2-(2-oxopyrrolidin-3-ylidene)acetates) 2 under relatively mild conditions (100 °C for 2–5 h under 40 atm of a 4:1 mixture of CO-air). This stereoselective multicomponent catalytic approach occurs through an ordered sequence of steps starting from simple building blocks, involving nitrogen palladation of the homopropargylic amine followed by CO insertion, intramolecular syn triple bond insertion with 5-exo-dig cyclization, further CO insertion and alcoholysis. The method has been successfully applied to a variety of differently substituted alkyne substrates and different alcohols (including MeOH, primary, secondary, and tertiary alcohols) to give the new α,β-unsaturated γ-lactam derivatives in 47–85% yields.

The biological evaluation of some of the novel α,β-unsaturated γ-lactams synthesized in this work, aimed at assessing their cytotoxicity toward tumor cells and their probable biomolecular targets, is currently underway in our laboratories and the results will be reported elsewhere.

Supplementary Materials: The following are available online at https://www.mdpi.com/2073-4344/11/2/227/s1: X-ray data for compounds 2a and 2b, Figure S1 (Molecular structure of methyl (Z)-2-(2-oxo-1-phenylpyrrolidin-3-ylidene)acetate 2a) and Figure S2 (Molecular structure of methyl (Z)-2-(1-(4-chlorophenyl)-2-oxopyrrolidin-3-ylidene)acetate 2b); Copies of HRMS, $^1$H NMR, and $^{13}$C($^1$H) NMR spectra for all substrates and products.

Author Contributions: Conceptualization, B.G., R.M., and I.Z.; methodology, R.M., I.Z., M.B., C.D.A., L.F., A.F., N.D.C., A.R.C., B.G.; validation, R.M., I.Z., M.B., C.D.A., L.F., A.F., N.D.C., A.R.C., B.G.; investigation, R.M., I.Z., M.B., C.D.A., L.F., A.F., N.D.C., A.R.C., B.G.; writing, B.G.; supervision, B.G.; funding acquisition, B.G. All authors have read and agreed to the published version of the manuscript.

Funding: Financial support by MIUR PRIN 2017YJMPZN project (Mussel-inspired functional biopolymers for underwater adhesion, surface/interface derivatization and nanostructure/composite self-assembly/MUSSEL) to B.G. is acknowledged.

Data Availability Statement: The data presented in this study are available on request from the corresponding author.

Acknowledgments: We thank Antonio Palumbo Piccionello (University of Palermo, Italy) for HRMS measurements.

Conflicts of Interest: The authors declare no conflict of interest.

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