

## Article

# A Stereoselective, Multicomponent Catalytic Carbonylative Approach to a New Class of $\alpha,\beta$ -Unsaturated $\gamma$ -Lactam Derivatives

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**Abstract:** We report a stereoselective, multicomponent catalytic carbonylative approach to a new class of  $\alpha,\beta$ -unsaturated  $\gamma$ -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 PdI<sub>2</sub> in conjunction with KI to give the  $\gamma$ -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 PdI<sub>2</sub> and 5–50 mol% of KI.

**Keywords:** carbonylation;  $\gamma$ -lactams; heterocycles; homogeneous catalysis; homopropargylic amines; multicomponent reaction; oxidative carbonylation; palladium; pyrrolidinones; stereoselective synthesis

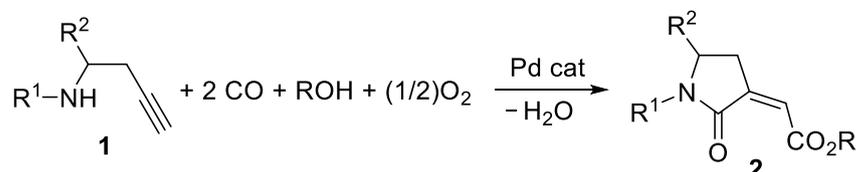
## 1. Introduction

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 CO<sub>2</sub> [6].

In this work, a stereoselective, multicomponent catalytic carbonylative approach to a new class of  $\alpha,\beta$ -unsaturated  $\gamma$ -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 PdI<sub>2</sub> 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-trichloroethoxycarbonyl chloride [12]. To the best of our knowledge, however, no method has been reported so far to synthesize the  $\gamma$ -lactam derivatives **2** disclosed in this work.



**Scheme 1.** Stereoselective multicomponent catalytic carbonylative synthesis of alkyl (Z)-2-(2-oxopyrrolidin-3-ylidene)acetates **2** from homopropargylic amines **1**.

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

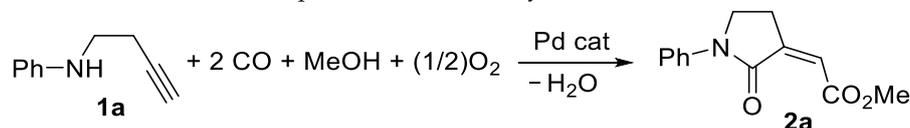
The synthetic method developed in our work for the preparation of new alkyl (Z)-2-(2-oxopyrrolidin-3-ylidene)acetate derivatives **2** is based on the oxidative carbonylation of readily available 3-yn-1-amines (homopropargylic amines) **1** carried out with the very simple PdI<sub>2</sub>/KI catalytic 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 O<sub>2</sub> (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 PdI<sub>2</sub> (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  $\gamma$ -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, <sup>1</sup>HNMR, and <sup>13</sup>CNMR 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 PdI<sub>2</sub>, and 64% yield with 0.5 mol% of PdI<sub>2</sub>; 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% PdI<sub>2</sub> (Table 2, entry 4). On the other hand, more hindered and less nucleophilic isopropanol led to a lower

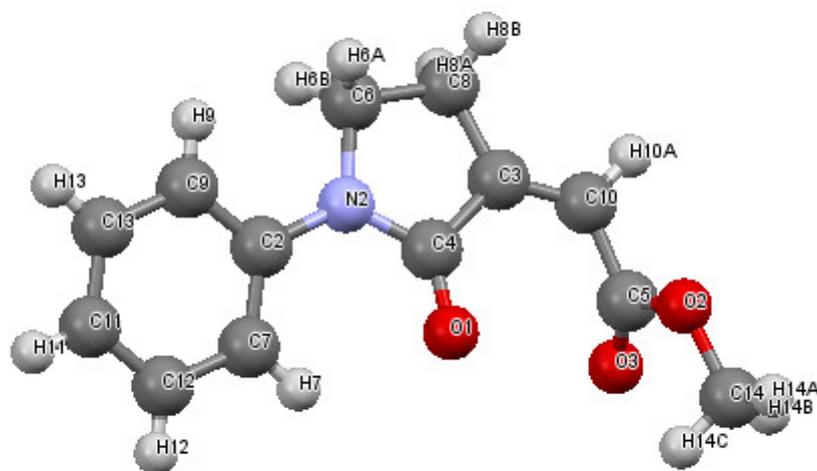
yield of the corresponding ester **2a''** (72%; Table 2, entry 5). With *tert*-butanol, the yield of **2a'''** was 33% (Table 2, entry 6), which, however, could be improved to 54% working under more diluted conditions (Table 2, entry 7).

**Table 1.** Optimization of carbonylation conditions <sup>a</sup>.



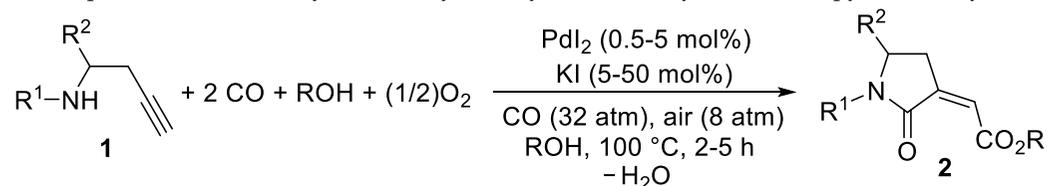
Entry	PdI <sub>2</sub> /KI/1a Molar Ratio	Concn of 1a <sup>b</sup>	T (°C)	t (h)	P <sub>CO</sub> (atm)	P <sub>air</sub> (atm)	Yield (%) <sup>c</sup>
1	1/10/20	0.04	100	2	32	8	74
2	1/5/20	0.04	100	2	32	8	65
3	1/2/20	0.04	100	2	32	8	55
4	1/10/20	0.04	100	2	48	12	66
5	1/10/20	0.04	100	2	16	4	67
6	1/10/20	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 <sup>d</sup>
10	1/10/20	0.04	100	8	32	8	33

<sup>a</sup> All reactions were carried out in MeOH. Unless otherwise noted, substrate conversion was quantitative in all cases. <sup>b</sup> Mmol of **1a** per mL of MeOH. <sup>c</sup> Isolated yield based on starting **1a**. <sup>d</sup> Substrate conversion was 85%.



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

Our next step was to verify the generality of the process using other differently substituted homopropargylic amines **1b–n** (Table 2, entries 8–27). Very good results were consistently obtained with all the tested *N*-aryl-substituted substrates **1b–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 **2b**, 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<sub>2</sub>) also for substrates **1b** (Table 2, entry 9), **1c** (Table 2, entry 11), and **1e** (Table 2, entry 14), still with satisfactory results. In fact, the yields of products **2b**, **2c**, and **2e** were only slightly inferior with respect to those obtained with 5 mol% of PdI<sub>2</sub> (Table 2; compare entries 9, 11, and 14 with entries 8, 10, and 13, respectively).

**Table 2.** Multicomponent PdI<sub>2</sub>/KI-catalyzed carbonylative synthesis of alkyl (Z)-2-(2-oxopyrrolidin-3-ylidene)acetates **2**<sup>a,b</sup>.

Entry	<b>1</b>	ROH	PdI <sub>2</sub> /KI/ <b>1</b> Molar Ratio	Substrate Concentration <sup>c</sup>	Time (h)	<b>2</b>	Yield of <b>2</b> (%) <sup>d</sup>
1		MeOH	1/10/20	0.1	2		85
2	<b>1a</b>	MeOH	1/10/100	0.1	2	<b>2a</b>	72
3	<b>1a</b>	MeOH	1/10/200	0.1	2	<b>2a</b>	64
4	<b>1a</b>	EtOH	1/10/20	0.1	2		82
5	<b>1a</b>	<i>i</i> PrOH	1/10/20	0.1	2		72
6	<b>1a</b>	<i>t</i> BuOH	1/10/20	0.1	2		33
7	<b>1a</b>	<i>t</i> BuOH	1/10/20	0.04	2	<b>2a'''</b>	54
8		MeOH	1/10/20	0.1	2		77
9	<b>1b</b>	MeOH	1/10/100	0.1	2	<b>2b</b>	72

Table 2. Cont.

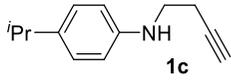
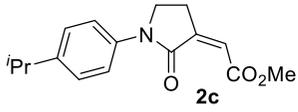
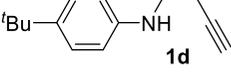
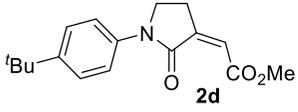
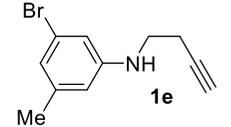
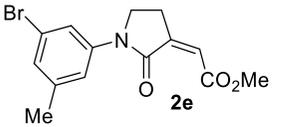
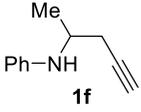
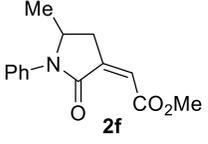
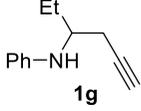
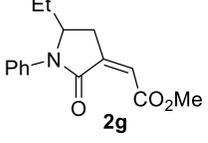
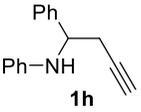
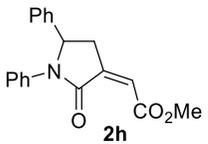
Entry	1	ROH	PdI <sub>2</sub> /KI/1 Molar Ratio	Substrate Concentration <sup>c</sup>	Time (h)	2	Yield of 2 (%) <sup>d</sup>
10		MeOH	1/10/20	0.1	2		74
11	<b>1c</b>	MeOH	1/10/100	0.1	2	<b>2c</b>	72
12		MeOH	1/10/20	0.1	2		70
13		MeOH	1/10/20	0.1	2		78
14	<b>1e</b>	MeOH	1/10/100	0.1	2	<b>2e</b>	75
15		MeOH	1/10/20	0.1	2		77
16		MeOH	1/10/20	0.1	2		78
17		MeOH	1/10/20	0.1	2		82

Table 2. Cont.

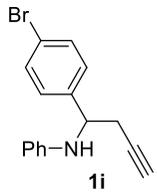
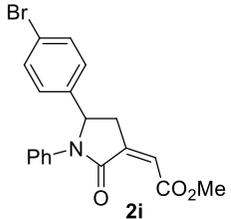
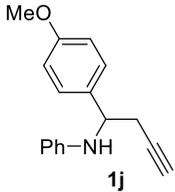
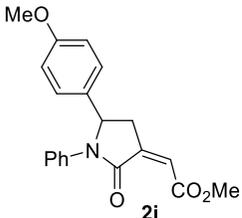
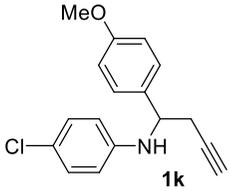
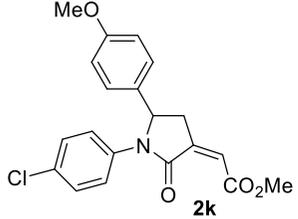
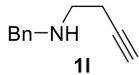
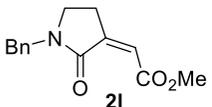
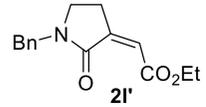
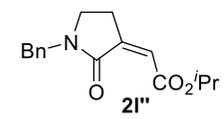
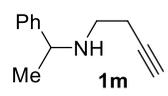
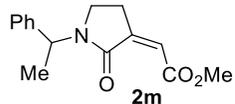
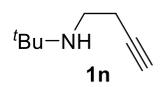
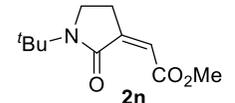
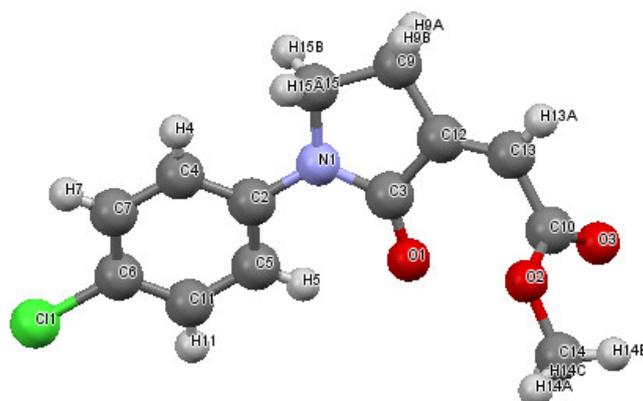
Entry	1	ROH	PdI <sub>2</sub> /KI/1 Molar Ratio	Substrate Concentration <sup>c</sup>	Time (h)	2	Yield of 2 (%) <sup>d</sup>
18		MeOH	1/10/20	0.1	2		70
19		MeOH	1/10/20	0.1	2		71
20		MeOH	1/10/20	0.1	2		70
21		MeOH	1/10/20	0.1	2		50
22	<b>1l</b>	EtOH	1/10/20	0.1	5		47

Table 2. Cont.

Entry	1	ROH	PdI <sub>2</sub> /KI/1 Molar Ratio	Substrate Concentration <sup>c</sup>	Time (h)	2	Yield of 2 (%) <sup>d</sup>
23	<b>1l</b>	<i>i</i> PrOH	1/10/20	0.1	5		48
24	<b>1l</b>	MeOH	1/10/20	0.04	2	<b>2l</b>	65
25		MeOH	1/10/20	0.1	2		52
26	<b>1m</b>	MeOH	1/10/20	0.04	2	<b>2m</b>	75
27		MeOH	1/10/20	0.04	5		47

<sup>a</sup> Unless otherwise noted, all reactions were carried out in ROH (MeOH, EtOH, *i*PrOH, or *t*BuOH) 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.

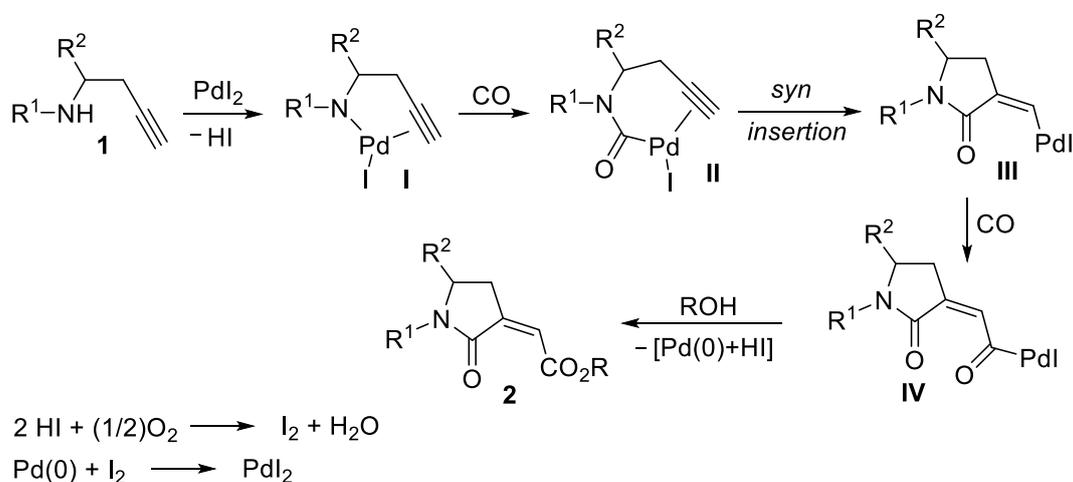
<sup>d</sup> Isolated yield based on starting **1**.



**Figure 2.** Molecular structure of methyl (Z)-2-(1-(4-chlorophenyl)-2-oxopyrrolidin-3-ylidene)acetate **2b**. The figure shows the atom labelling scheme for non-H atoms and displacement ellipsoids at the 50% probability level.

The carbonylation protocol led to lower  $\gamma$ -lactam yields when starting from *N*-alkyl substituted substrates, such as *N*-benzylbut-3-yn-1-amine **1l** 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 **2l** 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*-butyl)-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 PdI<sub>2</sub>/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 PdI<sub>2</sub> by the action of O<sub>2</sub>.



**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.  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra were recorded at 25 °C in  $\text{CDCl}_3$  at 300 MHz and 75 MHz, respectively, with  $\text{Me}_4\text{Si}$  as internal standard, using a Bruker DPX Avance 300 NMR Spectrometer (Bruker Italia s.r.l., Milano, Italy); chemical shifts ( $\delta$ ) 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 mode, and were recorded in the 150–1000  $m/z$  range. The LC-MS experimental conditions were as follows: The flow-rate was 0.4 mL/min and the column temperature was set to 30 °C. The eluents were formic acid–water (0.1:99.9,  $v/v$ ) (phase A) and formic acid–acetonitrile (0.1:99.9,  $v/v$ ) (phase B). The following gradient was employed: 0–10 min, linear gradient from 5% to 95% B; 10–15 min, washing and reconditioning of the column to 5% B. Injection volume was 10  $\mu\text{L}$ .  $\text{N}_2$  was employed as desolvation gas at 300 °C and a flow rate of 8 L/min. The nebulizer was set to 45 psig. The Sheat gas temperature was set at 400 °C and a flow of 12 L/min. A potential of 3.5 kV was used on the capillary for positive ion mode. The fragmentor was set to 175 V.

#### 3.2. Preparation of Substrates **1a–g** and **1l–n**

*N*-Substituted 3-yn-1-amines **1a–g** and **1l–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; 3-bromo-5-methylaniline, 5.58 g; benzylamine, 3.21 g;  $\alpha$ -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 **1n**; 4 h for **1l**; 5 h for **1m**; 24 h for **1a–1g**) under reflux under nitrogen. After cooling to room temperature, saturated  $\text{Na}_2\text{CO}_3$  aqueous solution and AcOEt were added to the mixture. The layers were separated and the aqueous layer was extracted with AcOEt (for **1a–g**, **1l–m**) or  $\text{Et}_2\text{O}$  (for **1n**) ( $3 \times 15$  mL). The combined organic layers were washed with brine, dried over  $\text{K}_2\text{CO}_3$ , filtered, and concentrated under vacuum (30 °C and 100 mbar for **1a–g**, **1l–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  $\text{CH}_2\text{Cl}_2$ –MeOH (**1l–1m**). In the case of **1n**, column chromatography with  $\text{Et}_2\text{O}$  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)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 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, NH), 3.31 (s, br, 2H,  $\text{NCH}_2\text{CH}_2$ ), 2.49 (td,

$J = 6.5, 2.5, 2\text{H}, \text{NCH}_2\text{CH}_2$ ), 2.03 (t,  $J = 2.5, 1\text{H}, \equiv\text{CH}$ );  $^{13}\text{C}\{^1\text{H}\}$  NMR ( $\text{CDCl}_3$ , 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):  $m/z = 145$  ( $\text{M}^+$ , 16), 106 (100); HRMS (ESI-TOF)  $m/z$ :  $[(\text{M} + \text{H})^+]$  calcd for  $\text{C}_{10}\text{H}_{12}\text{N}^+$ : 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):  $\nu = 3406$  (m, br), 3296 (s), 2117 (w), 1601 (s), 1504 (s), 1293 (m), 1262 (m), 1089 (m), 817 (s)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz):  $\delta = 7.16$ – $7.08$  (m, 2H, aromatic), 6.58–6.49 (m, 2H, aromatic), 3.95 (s, br, 1H, NH), 3.27 (t,  $J = 6.6, \text{NCH}_2\text{CH}_2$ ), 2.48 (td,  $J = 6.6, 2.6, 2\text{H}, \text{NCH}_2\text{CH}_2$ ), 2.05 (t,  $J = 2.6, 1\text{H}, \equiv\text{CH}$ );  $^{13}\text{C}\{^1\text{H}\}$  NMR ( $\text{CDCl}_3$ , 75 MHz):  $\delta = 146.1, 129.1$  (2C), 122.3, 114.2 (2C), 81.5, 70.3, 42.4, 19.0; GC-MS (EI, 70 eV):  $m/z = 179$  ( $\text{M}^+$ , 16), 142 (34), 140 (100); HRMS (ESI-TOF)  $m/z$ :  $[(\text{M} + \text{H})^+]$  calcd for  $\text{C}_{10}\text{H}_{11}\text{ClN}^+$ : 180.0575; found, 180.0578.

### 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):  $\nu = 3397$  (m, br), 3298 (m, br), 2118 (w), 1616 (s), 1519 (s), 1288 (m), 1259 (m), 1186 (m), 1051 (w), 822 (m)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz):  $\delta = 7.09$ – $7.01$  (m, 2 H, aromatic), 6.62–6.54 (m, 2 H, aromatic), 3.81 (s, br, 1H, NH), 3.29 (t,  $J = 6.7, \text{NCH}_2\text{CH}_2$ ), 2.80 (heptuplet, 1H,  $J = 6.9, \text{CH}_3\text{CHCH}_3$ ), 2.48 (td,  $J = 6.7, 2.6, 2\text{H}, \text{NCH}_2\text{CH}_2$ ), 2.02 (t,  $J = 2.6, 1\text{H}, \equiv\text{CH}$ ), 1.20 (d,  $J = 6.9, 6\text{H}, (\text{CH}_3)_2\text{CH}$ );  $^{13}\text{C}\{^1\text{H}\}$  NMR ( $\text{CDCl}_3$ , 75 MHz):  $\delta = 145.6, 138.4, 127.2$  (2C), 113.2 (2C), 81.9, 77.2, 70.0, 42.8, 33.1, 24.2, 19.2; GC-MS (EI, 70 eV):  $m/z = 187$  ( $\text{M}^+$ , 18), 148 (100); HRMS (ESI-TOF)  $m/z$ :  $[(\text{M} + \text{H})^+]$  calcd for  $\text{C}_{13}\text{H}_{18}\text{N}^+$ : 188.1434; found, 188.1444.

### 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):  $\nu = 3402$  (w, br), 3294 (m, br), 2118 (vw), 1616 (m), 1520 (s), 1261 (m), 1192 (m), 822 (m)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz):  $\delta = 7.26$ – $7.16$  (m, 2 H, aromatic), 6.63–6.53 (d,  $J = 8.6, 2\text{H}, \text{aromatic}$ ), 3.83 (s, br, 1H, NH), 3.28 (t,  $J = 6.5, 2\text{H}, \text{NCH}_2\text{CH}_2$ ), 2.46 (td,  $J = 6.5, 2.5, 2\text{H}, \text{NCH}_2\text{CH}_2$ ), 2.01 (t,  $J = 2.5, 1\text{H}, \equiv\text{CH}$ ), 1.27 (s, 9H, *t*-Bu);  $^{13}\text{C}\{^1\text{H}\}$  NMR ( $\text{CDCl}_3$ , 75 MHz):  $\delta = 145.2, 140.6, 126.0$  (2C), 112.9 (2C), 81.9, 70.0, 42.7, 33.8, 31.5 (3C), 19.2; GC-MS (EI, 70 eV):  $m/z = 201$  ( $\text{M}^+$ , 20), 186 (22), 162 (100), 147 (29); HRMS (ESI-TOF)  $m/z$ :  $[(\text{M} + \text{H})^+]$  calcd for  $\text{C}_{14}\text{H}_{20}\text{N}^+$ : 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):  $\nu = 3394$  (w, br), 3299 (m), 2119 (vw), 1517 (s), 1316 (m), 1100 (w), 1037 (w), 803 (m)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz):  $\delta = 7.29$ – $7.24$  (m, 1 H, aromatic), 7.01–6.94 (m, 1 H, aromatic), 6.55 (d,  $J = 8.2, 1\text{H}, \text{aromatic}$ ), 4.45 (s, br, 1H, NH), 3.34 (q,  $J = 6.6, \text{NCH}_2\text{CH}_2$ ), 2.51 (td,  $J = 6.6, 2.6, 2\text{H}, \text{NCH}_2\text{CH}_2$ ), 2.22 (s, 3H, Me), 2.06 (t,  $J = 2.6, 1\text{H}, \equiv\text{CH}$ );  $^{13}\text{C}\{^1\text{H}\}$  NMR ( $\text{CDCl}_3$ , 75 MHz):  $\delta = 142.1, 132.9, 129.0, 127.8, 111.4, 110.0, 81.4, 70.3, 42.6, 20.0, 19.0$ ; GC-MS (EI, 70 eV):  $m/z = 239$   $[(\text{M}+2)^+, 20]$ , 237 ( $\text{M}^+$ , 21), 200 (96), 198 (100), 119 (45); HRMS (ESI-TOF)  $m/z$ :  $[(\text{M} + \text{H})^+]$  calcd for  $\text{C}_{11}\text{H}_{13}\text{BrN}^+$ : 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):  $\nu = 3403$  (m), 3294 (m), 2116 (w), 1603 (s), 1506 (s), 1316 (s), 1255 (w), 1154 (w), 750 (s)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz):  $\delta = 7.22$ – $7.12$  (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,  $\text{NH} + \text{CHCH}_3$ ), 2.53–2.31 (m, 2H,  $\text{CH}_2\text{C}\equiv$ ), 2.03 (t,  $J = 2.6, 1\text{H}, \equiv\text{CH}$ ), 1.31 (d,  $J = 6.4, 3\text{H}, \text{Me}$ );  $^{13}\text{C}\{^1\text{H}\}$  NMR ( $\text{CDCl}_3$ , 75 MHz):  $\delta = 146.8, 129.4$  (2C), 117.6, 113.6 (2C), 80.9, 70.7, 47.0, 25.5, 20.0; GC-MS (EI, 70 eV):  $m/z = 159$  ( $\text{M}^+$ , 13), 120 (100); HRMS (ESI-TOF)  $m/z$ :  $[(\text{M} + \text{H})^+]$  calcd for  $\text{C}_{11}\text{H}_{14}\text{N}^+$ : 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):  $\nu = 3399$  (m), 3294 (m), 2114 (w), 1601 (s), 1504 (s), 1315 (m), 1281 (m), 1153 (w), 748 (m)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz):  $\delta = 7.23$ – $7.09$  (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,  $\text{CHCH}_3$ ), 2.51–2.36 (m, 2H,  $\text{NCH}_2\text{CH}_2$ ), 2.00 (t,  $J = 2.6$ , 1H,  $\equiv\text{CH}$ ), 1.84–1.52 (m, 2 H,  $\text{CH}_2\text{CH}_3$ ), 0.99 (t, 3H,  $\text{CH}_3$ );  $^{13}\text{C}\{^1\text{H}\}$  NMR ( $\text{CDCl}_3$ , 75 MHz):  $\delta = 147.2$ , 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):  $m/z = 173$  ( $\text{M}^+$ , 11), 134 (100); HRMS (ESI-TOF)  $m/z$ :  $[(\text{M} + \text{H})^+]$  calcd for  $\text{C}_{12}\text{H}_{16}\text{N}^+$ : 174.1277; found, 174.1300.

### 3.2.8. *N*-Benzylbut-3-yn-1-Amine **1l**

Yield: 1.2 g, 75% based on but-3-yn-1-yl tosylate. Yellow oil. IR (film):  $\nu = 3296$  (s), 2915 (m), 2836 (m), 2116 (w), 1454 (m), 1120 (m), 738 (s), 699 (m), 640 (s)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz):  $\delta = 7.37$ – $7.22$  (m, 5H, Ph), 3.82 (s, 2 H,  $\text{CH}_2\text{Ph}$ ), 2.80 (t,  $J = 6.5$ , 2H,  $\text{NCH}_2\text{CH}_2$ ), 2.42 (td,  $J = 6.5$ , 2.6, 2H,  $\text{NCH}_2\text{CH}_2$ ), 2.00 (t,  $J = 2.6$ , 1H,  $\equiv\text{CH}$ ), 1.74 (s, br, 1H, NH);  $^{13}\text{C}\{^1\text{H}\}$  NMR ( $\text{CDCl}_3$ , 75 MHz):  $\delta = 140.1$ , 128.4 (2C), 128.1 (2C), 127.0, 82.5, 69.6, 53.4, 47.3, 19.5; GC-MS (EI, 70 eV):  $m/z = 159$  ( $\text{M}^+$ , 1), 120 (58), 91 (100). HRMS (ESI-TOF)  $m/z$ :  $[(\text{M} + \text{H})^+]$  calcd for  $\text{C}_{11}\text{H}_{14}\text{N}^+$ : 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)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz):  $\delta = 7.35$ – $7.10$  (m, 5H, Ph), 3.80 (q,  $J = 6.6$ , 1H,  $\text{CHCH}_3$ ), 2.72–2.53 (m, 2H,  $\text{NCH}_2$ ), 2.40–2.27 (m, 2 H,  $\text{NCH}_2\text{CH}_2$ ), 1.98 (s, br, 1 H,  $\equiv\text{CH}$ ), 1.78 (s, br, 1H, NH), 1.36 (d,  $J = 6.6$ , 3H, Me);  $^{13}\text{C}\{^1\text{H}\}$  NMR ( $\text{CDCl}_3$ , 75 MHz):  $\delta = 145.4$ , 128.5 (2C), 127.0, 126.6 (2C), 82.6, 69.5, 57.7, 45.7, 24.4, 19.6; HRMS (ESI-TOF)  $m/z$ :  $[(\text{M} + \text{H})^+]$  calcd for  $\text{C}_{12}\text{H}_{16}\text{N}^+$ : 174.1277; found, 174.1301. 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):  $\nu = 3310$  (m), 2967 (s), 2866 (s), 2118 (w), 1450 (m), 1365 (m), 1060 (w), 633 (m)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz):  $\delta = 2.73$  (t,  $J = 6.7$ , 2H,  $\text{NCH}_2$ ), 2.37 (td,  $J = 6.7$ , 2.6, 2H,  $\text{CH}_2\text{C}\equiv$ ), 2.06–1.97 (m, 2 H,  $\equiv\text{CH} + \text{NH}$ ), 1.12 (s, 9H, *t*-Bu);  $^{13}\text{C}\{^1\text{H}\}$  NMR ( $\text{CDCl}_3$ , 75 MHz):  $\delta = 82.7$ , 69.4, 50.3, 41.2, 29.0 (3C), 20.5; HRMS (ESI-TOF)  $m/z$ :  $[(\text{M} + \text{H})^+]$  calcd for  $\text{C}_8\text{H}_{16}\text{N}^+$ : 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*-Benzylideneaniline, *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  $\text{Na}_2\text{SO}_4$  (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),  $\text{H}_2\text{O}$  (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  $\text{Et}_2\text{O}$  (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 K<sub>2</sub>CO<sub>3</sub>, 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):  $\nu = 3410$  (m), 3256 (m), 2114 (w), 1605 (s), 1512 (s), 1327 (m), 1265 (w), 756 (s) cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz):  $\delta = 7.45$ –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, CHPh), 4.41 (s, 1H, NH), 2.85–2.56 (m, 2H, CH<sub>2</sub>C≡), 2.06 (t, *J* = 2.6, 1H, ≡CH); <sup>13</sup>C{<sup>1</sup>H} NMR (CDCl<sub>3</sub>, 75 MHz):  $\delta = 147.0$ , 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<sup>+</sup>, 7), 182 (100), 104 (45); HRMS (ESI-TOF) *m/z*: [(M + H)<sup>+</sup>] calcd for C<sub>16</sub>H<sub>16</sub>N<sup>+</sup>: 222.1277; found, 222.1298. The spectroscopic data agreed with those reported [22].

### 3.3.2. *N*-(1-(4-Bromophenyl)but-3-yn-1-yl)aniline **1i**

Yield: 1.59 g, 53% based on starting *N*-(4-bromobenzylidene)aniline. Yellow oil. IR (film):  $\nu = 3402$  (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<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz):  $\delta = 7.45$  (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 CHPh), 4.39 (s, br, 1H, CHPh or NH), 2.82–2.55 (m, 2H, CH<sub>2</sub>C≡), 2.08 (t, *J* = 2.5, 1 H, ≡CH); <sup>13</sup>C{<sup>1</sup>H} NMR (CDCl<sub>3</sub>, 75 MHz):  $\delta = 146.6$ , 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)<sup>+</sup>, 9], 299 (M<sup>+</sup>, 10), 262 (96), 260 (100), 104 (57); HRMS (ESI-TOF) *m/z*: [(M + H)<sup>+</sup>] calcd for C<sub>16</sub>H<sub>15</sub>BrN<sup>+</sup>: 300.0382; found, 300.0420.

### 3.3.3. *N*-(1-(4-Bromophenyl)but-3-yn-1-yl)aniline **1j**

Yield: 1.45 g, 57% based on starting *N*-(4-methoxybenzylidene)aniline. Yellow oil. IR (film):  $\nu = 3402$  (m), 3287 (m), 2118 (vw), 1605 (s), 1505 (s), 1173 (m), 1099 (w), 1034 (w), 752 (m) cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz):  $\delta = 7.30$  (distorted d, *J* = 8.3, 2H, aromatic), 7.15–7.04 (m, 2H, aromatic), 6.85 (distorted d, *J* = 8.3, 2 H, aromatic), 6.71–6.62 (m, 1H, aromatic), 6.57–6.50 (m, 2H, aromatic), 4.48 (t, *J* = 6.0, 1 H, CHPh), 4.35 (s, br, 1H, NH), 3.75 (s, 3H, OMe), 2.80–2.52 (m, 2 H, CH<sub>2</sub>C≡), 2.05 (s, br, 1H, ≡CH); <sup>13</sup>C{<sup>1</sup>H} NMR (CDCl<sub>3</sub>, 75 MHz):  $\delta = 158.9$ , 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<sup>+</sup>, 9), 212 (100); HRMS (ESI-TOF) *m/z*: [(M + H)<sup>+</sup>] calcd for C<sub>17</sub>H<sub>18</sub>NO<sup>+</sup>: 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):  $\nu = 3410$  (m), 3294 (m), 2114 (vw), 1605 (s), 1504 (s), 1250 (s), 1173 (m), 1088 (w), 1034 (m), 818 (m) cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz):  $\delta = 7.32$ –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, CHPh + NH), 3.76 (s, 3H, OMe), 2.80–2.50 (m, 2H, CH<sub>2</sub>C≡), 2.07 (t, *J* = 2.5, 1H, ≡CH); <sup>13</sup>C{<sup>1</sup>H} NMR (CDCl<sub>3</sub>, 75 MHz):  $\delta = 159.0$ , 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<sup>+</sup>, 9), 245 (100); HRMS (ESI-TOF) *m/z*: [(M + H)<sup>+</sup>] calcd for C<sub>17</sub>H<sub>17</sub>ClNO<sup>+</sup>: 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 PdI<sub>2</sub> (9.0 mg, 2.5 × 10<sup>-2</sup> mmol), KI (41.5 mg, 2.5 × 10<sup>-1</sup> mmol) and a solution of **1** (0.5 mmol; **1a**, 72.6 mg;

**1b**, 89.8 mg; **1c**, 93.6 mg; **1d**, 100.7 mg; **1e**, 119.1 mg; **1f**, 79.6 mg; **1g**, 86.6 mg; **1h**, 110.7 mg; **1i**, 150.1 mg; **1j**, 125.7 mg; **1k**, 142.9 mg; **1l**, 79.6 mg; **1m**, 86.6 mg; **1n**, 62.6 mg) in MeOH (5 mL for **1a–k** and 12.5 mL for **1l–n**). 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 (2h for **1a–m** or 5h for **1n**) 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**, **2b**, **2e**, **2f**, **2l** and **2m**; hexane/AcOEt 8:2 for **2c**, **2d**, **2g**, **2h**, **2i**, **2j** and **2k**; only hexane to hexane/AcOEt 6:4 for **2n**.

#### 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):  $\nu = 1733$  (s), 1696 (s), 1597 (m), 1496 (m), 1398 (m), 1307 (m), 1238 (m), 762 (m)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz):  $\delta = 7.72$ – $7.62$  (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,  $\text{NCH}_2$ ), 3.85 (s, 3H,  $\text{CO}_2\text{Me}$ ), 2.92 (td,  $J = 6.6$ , 2.4, 2H,  $\text{NCH}_2\text{CH}_2$ );  $^{13}\text{C}\{^1\text{H}\}$  NMR ( $\text{CDCl}_3$ , 75 MHz):  $\delta = 167.3$ , 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)  $m/z$ :  $[(M + H)^+]$  calcd for  $\text{C}_{13}\text{H}_{14}\text{NO}_3^+$ : 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):  $\nu = 1733$  (s), 1696 (s), 1496 (m), 1394 (m), 1241 (m), 1085 (w), 1010 (w), 892 (w), 828 (m)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz):  $\delta = 7.68$ – $7.60$  (m, 2H, aromatic), 7.36–7.28 (m, 2H, aromatic), 6.19 (s, br, 1H, =CH), 3.91–3.78 (m, 2 H,  $\text{NCH}_2$ ), 3.85 (s, 3H,  $\text{CO}_2\text{Me}$ ), 2.93 (td,  $J = 7.1$ , 2.3, 2H,  $\text{NCH}_2\text{CH}_2$ );  $^{13}\text{C}\{^1\text{H}\}$  NMR ( $\text{CDCl}_3$ , 75 MHz):  $\delta = 167.1$ , 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)  $m/z$ :  $[(M + H)^+]$  calcd for  $\text{C}_{13}\text{H}_{13}\text{ClNO}_3^+$ : 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):  $\nu = 1734$  (s), 1696 (s), 1516 (m), 1398 (m), 1307 (w), 1239 (m), 1017 (m), 835 (m)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz):  $\delta = 7.62$ – $7.53$  (m, 2H, aromatic), 7.26–7.18 (m, 2H, n aromatic), 6.16 (t,  $J = 2.3$ , 1H, =CH), 3.86 (t,  $J = 6.4$ , 2 H,  $\text{NCH}_2$ ), 3.85 (s, 3H,  $\text{CO}_2\text{Me}$ ), 2.97–2.83 (m, 3H,  $\text{NCH}_2\text{CH}_2 + \text{CHMe}_2$ ), 1.22 (d,  $J = 7.0$ , 6H,  $\text{CH}(\text{CH}_3)_2$ );  $^{13}\text{C}\{^1\text{H}\}$  NMR ( $\text{CDCl}_3$ , 75 MHz):  $\delta = 167.4$ , 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)  $m/z$ :  $[(M + H)^+]$  calcd for  $\text{C}_{17}\text{H}_{20}\text{NO}_3^+$ : 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):  $\nu = 1736$  (s), 1690 (s), 1520 (m), 1396 (m), 1234 (m), 1080 (w), 1049 (m), 895 (m), 833 (s)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz):  $\delta = 7.62$ – $7.50$  (m, 2H, aromatic), 7.43–7.30 (m, 2H, aromatic), 6.15 (s, br, 1H, =CH), 3.92–3.75 (m, 2H,  $\text{NCH}_2$ ), 3.84 (s, 3H,  $\text{CO}_2\text{Me}$ ), 2.95–2.82 (m, 2H,  $\text{NCH}_2\text{CH}_2$ ), 1.30 (s, 9H, *t*-Bu);  $^{13}\text{C}\{^1\text{H}\}$  NMR ( $\text{CDCl}_3$ , 75 MHz):  $\delta = 167.3$ , 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)  $m/z$ :  $[(M + H)^+]$  calcd for  $\text{C}_{17}\text{H}_{22}\text{NO}_3^+$ : 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):  $\nu = 1733$  (s), 1699 (s), 1496 (m), 1411 (w), 1016 (w)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz):  $\delta = 7.47$  (s, 1 H, aromatic), 7.22–7.11 (m, 2 H, aromatic), 6.20 (t,  $J = 2.2$ , 1H, =CH), 3.87–3.75 (m, 2H,  $\text{NCH}_2$ ), 3.81 (s, 3H,  $\text{CO}_2\text{Me}$ ), 3.00 (td,  $J = 6.5$ , 2.4, 2H,  $\text{NCH}_2\text{CH}_2$ ), 2.34 (s, 3H,  $\text{CH}_3$ );  $^{13}\text{C}\{^1\text{H}\}$  NMR ( $\text{CDCl}_3$ , 75 MHz):  $\delta = 167.2$ , 165.0, 140.3, 137.7,

134.6, 134.0, 129.3, 129.0, 122.8, 121.4, 52.3, 46.8, 25.1, 20.8; HRMS (ESI-TOF)  $m/z$ :  $[(M + H)^+]$  calcd for  $C_{14}H_{15}BrNO_3^+$ : 324.0230; found, 324.0212.

#### 3.4.6. (Z)-Methyl 2-(5-Methyl-2-Oxo-1-Phenylpyrrolidin-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):  $\nu = 1733$  (s), 1705 (s), 1596 (m), 1496 (m), 1388 (s), 1239 (m), 1015 (w)  $cm^{-1}$ ;  $^1H$  NMR ( $CDCl_3$ , 300 MHz):  $\delta = 7.47$ – $7.33$  (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,  $CO_2Me$ ), 3.14 (ddd,  $J = 17.3$ , 7.7, 2.4, 1H, NCHMeCHH), 2.50 (ddd,  $J = 17.5$ , 4.3, 2.4, 1H, NCHMeCHH), 1.23 (d,  $J = 6.2$ , 2H,  $CH_3$ );  $^{13}C\{^1H\}$  NMR ( $CDCl_3$ , 75 MHz):  $\delta = 167.4$ , 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)  $m/z$ :  $[(M + H)^+]$  calcd for  $C_{14}H_{16}NO_3^+$ : 246.1125; found, 246.1130.

#### 3.4.7. (Z)-Methyl 2-(5-Ethyl-2-Oxo-1-Phenylpyrrolidin-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):  $\nu = 1733$  (s), 1671 (s), 1496 (m), 1394 (m), 1240 (m), 1016 (w)  $cm^{-1}$ ;  $^1H$  NMR ( $CDCl_3$ , 300 MHz):  $\delta = 7.47$ – $7.33$  (m, 4H, aromatic), 7.25–7.16 (m, 1H, aromatic), 6.17 (t,  $J = 2.3$ , 1H, =CH), 4.31–4.19 (m, 1H, NCHEt), 3.82 (s, 3H,  $CO_2Me$ ), 3.05 (ddd,  $J = 17.6$ , 7.9, 2.3, 1H, NCH(Et)CHH), 2.66–2.53 (m, 1H, NCH(Et)CHH), 1.81–1.63 (m, 1H, CHHCH<sub>3</sub>), 1.52–1.34 (m, 1H, CHHCH<sub>3</sub>), 0.83 (t,  $J = 7.4$ , 3H,  $CH_2CH_3$ );  $^{13}C\{^1H\}$  NMR ( $CDCl_3$ , 75 MHz):  $\delta = 167.4$ , 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)  $m/z$ :  $[(M + H)^+]$  calcd for  $C_{15}H_{18}NO_3^+$ : 260.1281; found, 260.1309.

#### 3.4.8. (Z)-Methyl 2-(2-Oxo-1,5-Diphenylpyrrolidin-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):  $\nu = 1732$  (s), 1697 (s), 1597 (w), 1492 (m), 1385 (m), 1242 (m), 1011 (m)  $cm^{-1}$ ;  $^1H$  NMR ( $CDCl_3$ , 300 MHz):  $\delta = 7.48$ – $7.40$  (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,  $CO_2Me$ ), 3.39 (ddd,  $J = 17.2$ , 8.3, 2.3, 1H, NCHPhCHH), 2.73 (ddd,  $J = 17.2$ , 3.6, 2.3, 1H, NCH(Ph)CHH);  $^{13}C\{^1H\}$  NMR ( $CDCl_3$ , 75 MHz):  $\delta = 167.1$ , 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)  $m/z$ :  $[(M + H)^+]$  calcd for  $C_{19}H_{18}NO_3^+$ : 308.1281; found, 308.1286.

#### 3.4.9. (Z)-Methyl 2-(5-(4-Bromophenyl)-2-Oxo-1-Phenylpyrrolidin-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):  $\nu = 1736$  (s), 1697 (s), 1612 (w), 1489 (m), 1389 (m), 1250 (s), 1180 (w), 1026 (w), 833 (m)  $cm^{-1}$ ;  $^1H$  NMR ( $CDCl_3$ , 300 MHz):  $\delta = 7.45$ – $7.35$  (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 (dd,  $J = 8.3$ , 3.8, 1H, CHAr), 3.86 (s, 3H,  $CO_2Me$ ), 3.39 (ddd,  $J = 17.2$ , 8.3, 2.3, 1H, CHHC=), 2.69 (ddd,  $J = 17.2$ , 3.8, 2.3, 1H, CHHC=);  $^{13}C\{^1H\}$  NMR ( $CDCl_3$ , 75 MHz):  $\delta = 167.0$ , 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)  $m/z$ :  $[(M + H)^+]$  calcd for  $C_{19}H_{17}BrNO_3^+$ : 386.0386; found, 386.0384.

#### 3.4.10. (Z)-Methyl 2-(5-(4-Methoxyphenyl)-2-Oxo-1-Phenylpyrrolidin-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):  $\nu = 1721$  (s), 1697 (s), 1597 (m), 1512 (m), 1427 (w), 1373 (m), 1103 (m), 1034 (m), 1003 (m), 895 (m), 841 (m), 772 (m)  $cm^{-1}$ ;  $^1H$  NMR ( $CDCl_3$ , 300 MHz):  $\delta = 7.50$ – $7.34$  (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 (dd,  $J = 7.8$ , 3.6, 1H, CHAr), 3.86 (s, 3H,  $CO_2Me$ ), 3.73 (s, 3H, OMe), 3.44–3.25 (m, 1H, CHHC=), 2.81–2.60 (m, 1H, CHHC=);  $^{13}C\{^1H\}$  NMR ( $CDCl_3$ , 75 MHz):  $\delta = 167.2$ , 164.9, 159.3, 137.7, 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)  $m/z$ :  $[(M + H)^+]$  calcd for  $C_{20}H_{20}NO_4^+$ : 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):  $\nu = 1736$  (s), 1695 (s), 1613 (w), 1511 (m), 1690 (m), 1389 (m), 1249 (s), 1180 (m), 1011 (m), 895 (w), 833 (m)  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ , 300 MHz):  $\delta = 7.43$ – $7.34$  (m, 2H, aromatic), 7.25–7.15 (m, 2H, aromatic), 7.15–7.05 (m, 2H, aromatic), 6.87–6.76 (m, 2H, aromatic), 6.19 (s, br, 1H, =CH), 5.19 (dd,  $J = 8.0, 3.6$ , 1H, CHAr), 3.87 (s, 3H,  $\text{CO}_2\text{Me}$ ), 3.75 (s, 3H, OMe), 3.37 (ddd,  $J = 17.1, 8.0, 2.3$ , 1H, CHHC=), 2.73 (ddd,  $J = 17.1, 3.6, 2.3$ , 1H, CHHC=);  $^{13}\text{C}\{^1\text{H}\}$  NMR ( $\text{CDCl}_3$ , 75 MHz):  $\delta = 167.0, 164.9, 159.4, 137.3, 136.1, 132.2, 130.8, 128.8$  (2C), 127.2 (2C), 123.6 (2C), 123.5, 114.6 (2C), 60.3, 55.3, 52.4, 35.7; HRMS (ESI-TOF)  $m/z$ :  $[(M + H)^+]$  calcd for  $\text{C}_{20}\text{H}_{19}\text{ClNO}_4^+$ : 372.0997; found, 372.0995.

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

Yield: 79.7 mg, starting from 79.6 mg of **1l** (65%) (Table 2, entry 24). Yellow oil. IR (film):  $\nu = 1736$  (s), 1686 (s), 1497 (w), 1438 (m), 1338 (w), 1245 (m), 702 (m)  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ , 300 MHz):  $\delta = 7.37$ – $7.21$  (m, 5H, Ph), 6.11 (t,  $J = 2.4$ , 1H, =CH), 4.51 (s, 2H,  $\text{CH}_2\text{Ph}$ ), 3.86 (s, 3H,  $\text{CO}_2\text{Me}$ ), 3.29 (t,  $J = 6.5$ , 2H,  $\text{NCH}_2$ ), 2.76 (td,  $J = 6.5, 2.4$ , 2H,  $\text{NCH}_2\text{CH}_2$ );  $^{13}\text{C}\{^1\text{H}\}$  NMR ( $\text{CDCl}_3$ , 75 MHz):  $\delta = 167.4, 165.2, 138.4, 135.7, 128.8$  (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  $\text{C}_{14}\text{H}_{16}\text{NO}_3^+$ : 246.1130; found, 246.1128.

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

Yield: 97.2 mg, starting from 86.6 mg of **1m** (75%) (Table 2, entry 26). Yellow oil. IR (film):  $\nu = 1733$  (s), 1690 (s), 1423 (m), 1331 (w), 1234 (m), 1017 (w)  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ , 300 MHz):  $\delta = 7.43$ – $7.15$  (m, 5H, Ph), 6.08 (dist t,  $J = 2.3$ , 1H, =CH), 5.56 (q,  $J = 7.1$ , 1H,  $\text{CHMe}_2$ ), 3.86 (s, 3H,  $\text{CO}_2\text{Me}$ ), 3.42–3.30 (m, 1H,  $\text{NCHHCH}_2$ ), 3.08–2.94 (m, 1H,  $\text{NCHHCH}_2$ ), 2.83–2.60 (2H,  $\text{NCH}_2\text{CH}_2$ ), 1.55 (d,  $J = 7.1$ , 3H,  $\text{CH}_3$ );  $^{13}\text{C}\{^1\text{H}\}$  NMR ( $\text{CDCl}_3$ , 75 MHz):  $\delta = 167.4, 164.8, 139.4, 138.9, 128.6$  (2C), 127.7, 127.3 (2C), 121.5, 52.3, 49.7, 39.3, 24.3, 16.0; HRMS (ESI-TOF)  $m/z$ :  $[(M + H)^+]$  calcd for  $\text{C}_{15}\text{H}_{18}\text{NO}_3^+$ : 260.1281; found, 260.1290.

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

Yield: 49.7 mg, starting from 62.6 mg of **1n** (47%) (Table 2, entry 27). Yellow solid, mp 85–86 °C. IR (KBr):  $\nu = 1721$  (s), 1667 (s), 1412 (m), 1335 (m), 1211 (m), 1011 (s), 895 (m), 833 (m)  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ , 300 MHz):  $\delta = 5.97$  (t,  $J = 2.2$ , 1H, =CH), 3.84 (s, 3H,  $\text{CO}_2\text{Me}$ ), 3.50 (t,  $J = 6.4$ , 2H,  $\text{NCH}_2$ ), 2.72 (td,  $J = 6.4, 2.2$ , 2H,  $\text{NCH}_2\text{CH}_2$ ), 1.43 (s, 9H, *t*-Bu);  $^{13}\text{C}\{^1\text{H}\}$  NMR ( $\text{CDCl}_3$ , 75 MHz):  $\delta = 167.8, 165.6, 140.4, 120.2, 54.8, 52.2, 42.5, 27.4$  (3C), 24.3; HRMS (ESI-TOF)  $m/z$ :  $[(M + H)^+]$  calcd for  $\text{C}_{11}\text{H}_{18}\text{NO}_3^+$ : 212.1281; found, 212.1262.

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  $\text{PdI}_2$  (9.0 mg,  $2.5 \times 10^{-2}$  mmol), KI (41.5 mg,  $2.5 \times 10^{-1}$  mmol) and a solution of **1** (0.5 mmol; **1a**, 72.6 mg; **1f**, 79.6 mg) in EtOH or *iso*PrOH (5 mL) or *tert*-BuOH (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):  $\nu = 1728$  (s), 1690 (s), 1598 (w), 1496 (m), 1398 (m), 1306 (m), 1234 (m), 1095 (w), 1030 (m), 761 (m)  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ , 300 MHz):  $\delta = 7.70$ – $7.63$  (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), 4.33 (q,  $J = 7.2$ , 2 H,  $\text{CO}_2\text{CH}_2\text{CH}_3$ ), 3.85 (t,  $J = 6.6$ , 2H,  $\text{NCH}_2$ ), 2.90 (td,  $J = 6.6$ , 2.2, 2H,  $\text{NCH}_2\text{CH}_2$ ), 7.16 (t,  $J = 7.2$ , 3H,  $\text{CH}_2\text{CH}_3$ );  $^{13}\text{C}\{^1\text{H}\}$  NMR ( $\text{CDCl}_3$ , 75 MHz):  $\delta = 166.8$ , 164.4, 139.1, 138.3, 128.9 (2C), 125.1, 123.1, 119.7 (2C), 61.3, 45.2, 24.1, 14.1; HRMS (ESI-TOF)  $m/z$ :  $[(M + H)^+]$  calcd for  $\text{C}_{14}\text{H}_{16}\text{NO}_3^+$ : 246.1125; found, 246.1138.

### 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):  $\nu = 1723$  (s), 1699 (s), 1598 (w), 1496 (m), 1398 (m), 1306 (m), 1241 (m), 1106 (m), 970 (w), 762 (m)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz):  $\delta = 7.66$  (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,  $\text{CHMe}_2$ ), 3.82 (t,  $J = 6.5$ , 2H,  $\text{NCH}_2$ ), 2.92–2.80 (m, 2H,  $\text{NCH}_2\text{CH}_2$ ), 1.34 (d,  $J = 6.1$ , 6H,  $\text{CH}(\text{CH}_3)_2$ );  $^{13}\text{C}\{^1\text{H}\}$  NMR ( $\text{CDCl}_3$ , 75 MHz):  $\delta = 166.2$ , 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  $\text{C}_{15}\text{H}_{18}\text{NO}_3^+$ : 260.1281; found, 260.1290.

### 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):  $\nu = 1723$  (s), 1699 (s), 1598 (w), 1496 (m), 1400 (m), 1307 (m), 1251 (m), 1161 (m), 759 (w)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz):  $\delta = 7.67$  (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,  $\text{NCH}_2$ ), 2.92–2.80 (m, 2H,  $\text{NCH}_2\text{CH}_2$ ), 1.57 (s, 9H, *t*-Bu);  $^{13}\text{C}\{^1\text{H}\}$  NMR ( $\text{CDCl}_3$ , 75 MHz):  $\delta = 165.8$ , 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  $\text{C}_{16}\text{H}_{20}\text{NO}_3^+$ : 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):  $\nu = 1728$  (s), 1690 (s), 1668 (s), 1446 (w), 1337 (w), 1230 (m), 1030 (m)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz):  $\delta = 7.38$ –7.18 (m, 5H, Ph), 6.11 (t,  $J = 2.4$ , 1H, =CH), 4.51 (s, 2H,  $\text{CH}_2\text{Ph}$ ), 4.34 (q,  $J = 7.1$ , 2H,  $\text{CH}_2\text{CH}_3$ ), 3.29 (t,  $J = 6.4$ , 2H,  $\text{NCH}_2$ ), 2.76 (td,  $J = 6.4$ , 2.4, 2H,  $\text{NCH}_2\text{CH}_2$ ), 1.36 (t,  $J = 7.1$ , 3H,  $\text{CH}_2\text{CH}_3$ );  $^{13}\text{C}\{^1\text{H}\}$  NMR ( $\text{CDCl}_3$ , 75 MHz):  $\delta = 166.8$ , 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  $\text{C}_{15}\text{H}_{18}\text{NO}_3^+$ : 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):  $\nu = 1725$  (s), 1696 (s), 1496 (w), 1446 (m), 1238 (s), 1108 (m), 970 (w)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz):  $\delta = 7.37$ –7.20 (m, 5H, Ph), 6.12–6.06 (m, 1H, =CH), 5.22 (heptuplet,  $J = 6.3$ , 1H,  $\text{CHMe}_2$ ), 4.51 (s, 2H,  $\text{CH}_2\text{Ph}$ ), 3.27 (t,  $J = 6.5$ , 2H,  $\text{NCH}_2$ ), 2.74 (td,  $J = 6.5$ , 2.3, 2H,  $\text{NCH}_2\text{CH}_2$ ), 1.36 (d,  $J = 6.3$ , 6H,  $\text{CH}(\text{CH}_3)_2$ );  $^{13}\text{C}\{^1\text{H}\}$  NMR ( $\text{CDCl}_3$ , 75 MHz):  $\delta = 166.3$ , 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  $\text{C}_{16}\text{H}_{20}\text{NO}_3^+$ : 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  $\text{PdI}_2$  (54.0 mg,  $1.5 \times 10^{-1}$  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 as 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<sub>2</sub>-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  $\alpha,\beta$ -unsaturated  $\gamma$ -lactam derivatives in 47–85% yields.

The biological evaluation of some of the novel  $\alpha,\beta$ -unsaturated  $\gamma$ -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, <sup>1</sup>H NMR, and <sup>13</sup>C{<sup>1</sup>H} NMR spectra for all substrates and products.

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