

Article

Synthesis of 3-alkylideneisoindolin-1-ones via Sonogashira cyclocarbonylative reactions of 2-ethynylbenzamides

Gianluigi Albano, Stefano Giuntini, and Laura Antonella Aronica

J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.0c01282 • Publication Date (Web): 03 Jul 2020

Downloaded from pubs.acs.org on July 8, 2020

Just Accepted

"Just Accepted" manuscripts have been peer-reviewed and accepted for publication. They are posted online prior to technical editing, formatting for publication and author proofing. The American Chemical Society provides "Just Accepted" as a service to the research community to expedite the dissemination of scientific material as soon as possible after acceptance. "Just Accepted" manuscripts appear in full in PDF format accompanied by an HTML abstract. "Just Accepted" manuscripts have been fully peer reviewed, but should not be considered the official version of record. They are citable by the Digital Object Identifier (DOI®). "Just Accepted" is an optional service offered to authors. Therefore, the "Just Accepted" Web site may not include all articles that will be published in the journal. After a manuscript is technically edited and formatted, it will be removed from the "Just Accepted" Web site and published as an ASAP article. Note that technical editing may introduce minor changes to the manuscript text and/or graphics which could affect content, and all legal disclaimers and ethical guidelines that apply to the journal pertain. ACS cannot be held responsible for errors or consequences arising from the use of information contained in these "Just Accepted" manuscripts.

Synthesis of 3-alkylideneisoindolin-1-ones via Sonogashira cyclocarbonylative reactions of 2-ethynylbenzamides

Gianluigi Albano,^{a,b} Stefano Giuntini^{c,d} and Laura Antonella Aronica^{a,*}

a. Dipartimento di Chimica e Chimica Industriale, Università di Pisa, Via Giuseppe Moruzzi 13, 56124 Pisa, Italy.

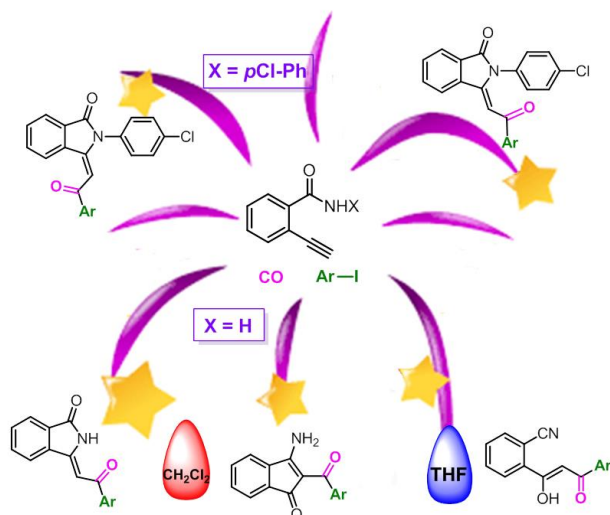
b. Present address: Dipartimento di Chimica, Università degli Studi di Bari “Aldo Moro”, Via Edoardo Orabona 4, 70126 Bari, Italy.

c. Dipartimento di Chimica “Ugo Schiff”, Università degli Studi di Firenze, Via della Lastruccia 3, 50019 Sesto Fiorentino, Italy.

d. Centro di Risonanze Magnetiche (CERM), Università degli Studi di Firenze and Consorzio Interuniversitario Risonanze Magnetiche di Metallo Proteine (CIRMMMP), Via Luigi Sacconi 6, 50019 Sesto Fiorentino, Italy

* Corresponding author: laura.antonella.aronica@unipi.it

TOC graphic:



ABSTRACT

Cyclocarbonylative Sonogashira reactions of *ortho*-ethynylbenzamides have been investigated. The process is carried out under CO pressure, in the presence of a very small amount of PdCl₂(PPh₃)₂ (0.4 mol %) as a catalytic precursor, and without the need for a Cu salt as co-catalyst. 2-Ethynylbenzamide reacted successfully with iodoarenes bearing electron-withdrawing and electron-donating groups giving rise to different classes of compounds depending on the solvent used. On the contrary, *N*-(4-chlorophenyl)-2-ethynylbenzamide afforded exclusively polyfunctionalized isoindolinones with high stereoselectivity towards (*E*) isomers.

INTRODUCTION

N-containing heterocycles are structural motifs frequently found in a large number of biologically active compounds. For instance, isoindolinone is the core structural unit in several natural products such as chilenine,¹ lennoxamine,² nuevamine,³ chaetosisoindolinone,⁴ stachybotrisan,⁵ erinacerin,⁶ meyeroguilline⁷ and caputmedusin.⁸ In particular, 3-methyleneisoindolin-1-ones have been recognized as nuclei of natural and synthetic compounds such as fumaridine,⁹ narceine imide,¹⁰ stigmalactam,¹¹ magallinesine,¹² chartarlactam L,¹³ aristoyagonine,¹⁴ aristolactams¹⁵ and AKS-186.¹⁶ These heterocycles have been found to possess antimycobacterial¹⁷ and antifungal¹⁸ activities, antiplatelet^{11,19} properties, to act as anti-inflammatory²⁰⁻²² and neuroprotective²³ agents, to inhibit vasoconstriction,^{24,25} and to show cytotoxic and antitumoral activities.²⁶⁻³⁰

Owing to their great importance, there has been a continuous interest in developing metal-promoted cyclization methods for the syntheses of 3-methyleneisoindolin-1-ones.³¹ Transition-metal-catalysed cyclocarbonylation reaction is a useful approach to the formation of lactame moiety.³²⁻⁴¹ Mancuso and co-workers developed an interesting synthesis of 3-methyleneisoindolin-1-ones based on a PdI₂-catalyzed cyclization of 2-alkynylbenzamides with secondary amines under oxidative carbonylation conditions;^{42,43} Huang⁴⁴ and Hua⁴⁵ proposed cyclocarbonylation of ketimines under CO pressure as

valuable approach to isoindolinones; Wu's group⁴⁶ described an elegant procedure based on the cyclization of arylketimine using Mo(CO)₆ as CO source and Jiang and co-workers⁴⁷ developed a palladium-catalyzed carbonylation reaction of aromatic oxime for the synthesis of isoindolinones derivatives.

In the last years, our research group have acquired a large experience in the synthesis of heterocyclic compounds via transition metal-promoted cyclocarbonylative coupling.⁴⁸⁻⁵³ Due to the large interest of isoindolinone scaffold, in the present work we explored a new approach for the synthesis of 3-alkylideneisoindolin-1-ones via copper-free Pd-catalysed Sonogashira cyclocarbonylative reaction⁵⁴⁻⁵⁸ between 2-ethynylbenzamides and various iodoarenes.

RESULTS AND DISCUSSION

We started our study with the synthesis of 2-ethynylbenzamide (**1**), which was easily obtained from commercially available 2-bromobenzamide according to a sequence of Sonogashira reaction with trimethylsilylacetylene and following desilylation process performed with CsF in MeOH (Scheme S1 in Supporting Information). Then, the first cyclocarbonylative Sonogashira reaction was carried out with equimolar quantities of 2-ethynylbenzamide **1** and iodobenzene **2a**, in a stainless steel autoclave placed under CO pressure (20 atm) using a very low amount of PdCl₂(PPh₃) (0.4 mol%), a mixture of CH₂Cl₂ and triethylamine for 4 h at 100 °C (Table 1, entry 1). Analysis of the ¹H-NMR spectrum of the crude product showed the partial conversion of precursors and the presence of proton signals that indicated the formation of two different compounds. The first product was the expected 3-(2-oxo-2-phenylethylidene)isoindolin-1-one **3a**, recovered chemically pure with 34% of yield. Its structure was confirmed by spectroscopic (¹H-NMR and ¹³C-NMR), spectrometric (LC-MS) and elemental analysis (see Experimental Section). Moreover, NOE (Nuclear Overhauser Effect) experiments (Figure 1, A) highlighted not only a strong dipolar coupling between the vinyl proton H^a and the aromatic protons H^b and H^c but also the absence of interactions of the amide proton H^e with other hydrogens. These

evidences allowed the attribution of *Z* configuration to **3a** obtained also as a single conformational isomer, the *s*-cis, probably due to hydrogen bond between amide proton and carbonyl oxygen (Figure 1, A).

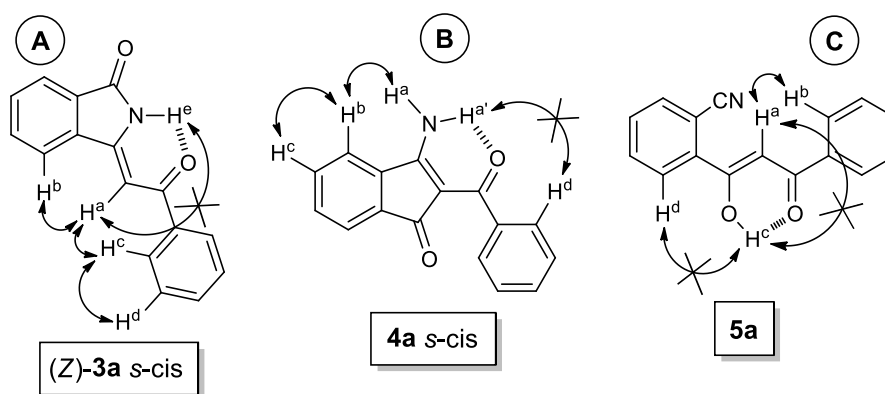


Figure 1. Chemical structure of the products of cyclocarbonylative Sonogashira reaction between **1** and **2a**: A) 3-(2-oxo-2-phenylethylidene)isoindolin-1-one **3a**; B) 3-amino-2-benzoyl-1*H*-inden-1-one **4a**; C) (*Z*)-2-(1-hydroxy-3-oxo-3-phenylprop-1-en-1-yl)benzonitrile **5a**.

The second product (21% yield), required a more in-depth structural study. First, the analysis of the ^1H -NMR spectrum highlighted the presence of two broad singlet signals at particularly low fields (10.09 and 10.21) which were attributed to amino protons $\text{H}^{\text{a,a'}}$ (Figure 1, B). Moreover, ^{13}C -NMR spectrum indicated the presence of two signals corresponding to two carbonyl carbons (186.73 ppm and 190.22 ppm). Two peaks corresponding to a double bond were also detected: the first at 172.21 ppm was related to a carbon atom linked to NH_2 group and the other at 103.02 ppm was due to $\equiv\text{C}-\text{CO}$. All these data confirmed the formation of 3-amino-2-benzoyl-1*H*-inden-1-one **4a** (Table 1, entry 1). Moreover, NOE experiments conducted on the pure product highlighted a dipolar coupling between the protons H^{a} , H^{b} and H^{c} and the absence of couplings between $\text{H}^{\text{c'}}$ and H^{d} (Figure 1, B), thus indicating also for product **4a** a *s*-cis conformation.

With the aim to increase the conversion and the selectivity towards desired compound **3a**, cyclocarbonylative Sonogashira tests at different reaction times, temperatures and amounts of catalytic precursor were performed. As is evident from the results described in Table 1, increasing the reaction time from 4 to 8 hours (Table 1, entry 2) or the amount of $\text{PdCl}_2(\text{PPh}_3)_2$ (Table 1, entry 3, 1 mol%) did

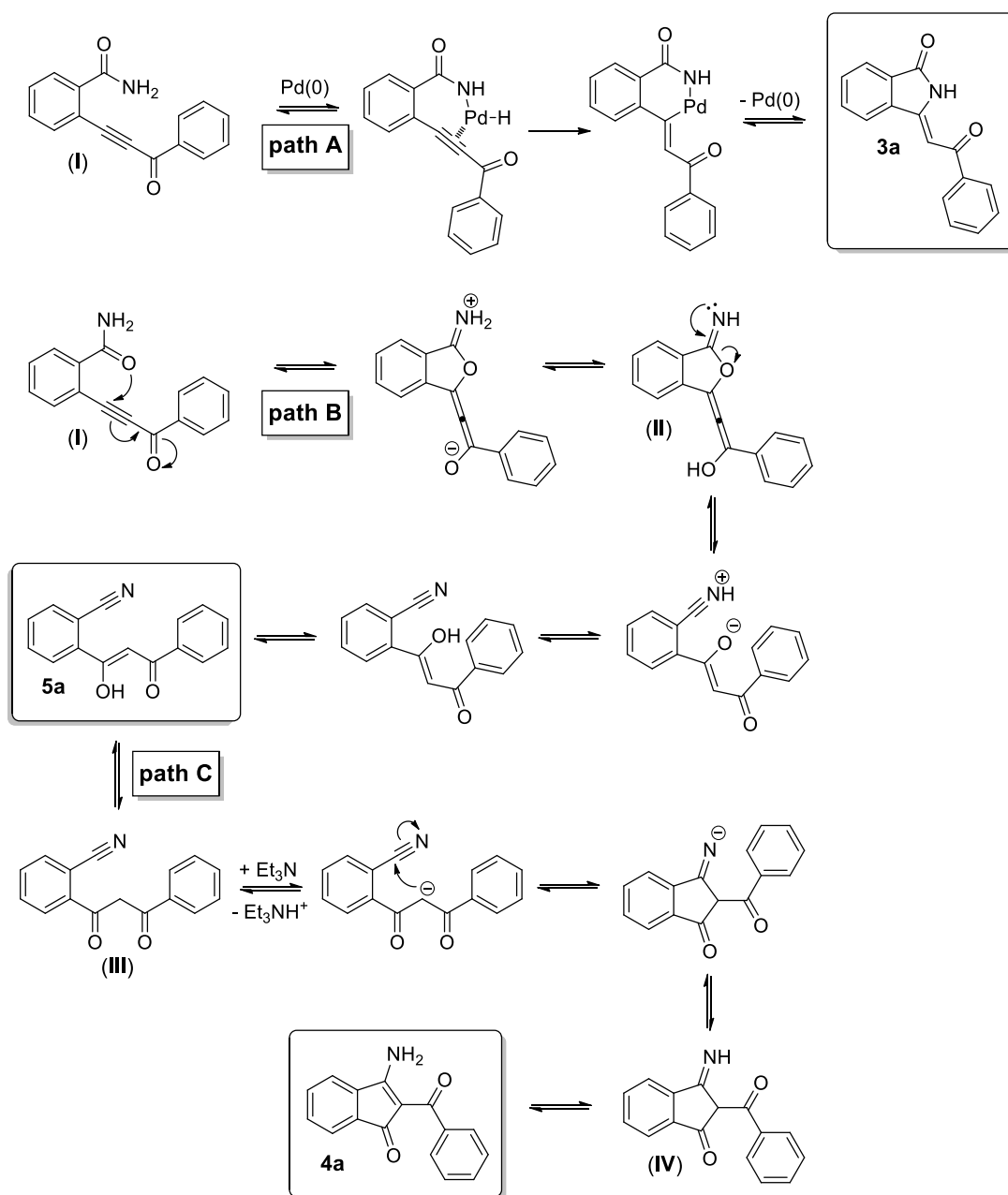
not affect the conversion significantly. On the contrary, an increase in selectivity towards the amino product **4a** was observed (up to ~ 70%). A similar result was obtained by conducting the reaction at 70 °C for 24 h (Table 1, entry 4).

Table 1. Optimization study of the cyclocarbonylative Sonogashira reaction between 2-ethynylbenzamide **1** and iodobenzene **2a**.

Entry ^a	Solvent	T (°C)	t (h)	Conversion ^b (%)	Selectivity ^c (%)		
					3a	4a	5a
1	CH ₂ Cl ₂	100	4	80	57 (34)	43 (21)	/
2	CH ₂ Cl ₂	100	8	78	39	61	/
3 ^d	CH ₂ Cl ₂	100	4	69	28	72	/
4	CH ₂ Cl ₂	70	24	79	29	71	/
5	CH ₂ Cl ₂	50	24	78	21	/	79 (42)
6	THF	100	4	94	29	/	71 (44)
7	THF	50	24	79	21	/	79
8	THF	30	24	16	26	/	74
9	CH ₃ CN	100	4	85	78	/	22
10	CH ₃ CN	50	24	83	38	/	62
11	DMF	100	4	100	33	32	35

a) All reactions were carried with 2-ethynylbenzamide **1** (1.0 mmol), iodobenzene **2a** (1.0 mmol), CO (20 atm), PdCl₂(PPh₃)₂ (0.4 mol%), Et₃N (1.5 mL) and the solvent (4.0 mL), unless otherwise stated. **b)** Conversion was determined by ¹H-NMR peak integration on the crude product. **c)** Selectivity was estimated by ¹H-NMR spectroscopy; isolated yields of pure products are reported in parentheses. **d)** Reaction performed with 1 mol% of PdCl₂(PPh₃)₂.

A further reduction in temperature to 50 °C (Table 1, entry 5) gave instead an unexpected result. The analysis of the ^1H -NMR spectrum of the crude product showed, in addition to the presence of the isoindolinonic derivative **3a**, the disappearance of the typical signals of **4a** and the appearance of a new olefinic proton signal at 6.95 ppm. After purification the new compound was subjected to ^1H -NMR, ^{13}C NMR, LC-MS and elemental analyses in order to determine its exact structure, which resulted to be (Z)-2-(1-hydroxy-3-oxo-3-phenylprop-1-en-1-yl)benzonitrile **5a** (Figure 1, C). In fact, analysis of ^1H -NMR spectrum indicated the presence of a signal that resonates at very low fields (16.44 ppm), characteristic of a 1,3-diketonic system in enolic form.⁵⁹ Furthermore, in the ^{13}C -NMR spectrum, an olefinic carbon (96.00 ppm), a signal corresponding to $\text{C}\equiv\text{N}$ (118.00 ppm) and two peaks at 183.14 and 186.21 ppm (carbonyl and enolic carbon atoms) were clearly observed, thus confirming the structure of **5a** (42% yield of isolated product). The formation of the three products **3a**, **4a** and **5a** can be tentatively explained by the mechanism described in Scheme 1. First, expected isoindolin-1-one **3a** was generated via initial formation of the Sonogashira product (**I**), which is *in situ* cyclized as previously observed (Scheme 1, path A).^{48,49} On the other hand, in the case of **4a** a process of addition of carbonyl oxygen to the triple bond can be hypothesized with formation of an allenyl species (**II**). After prototropic exchange and subsequent opening of the cycle, 1,3-diketone **5a** in enolic form can be generated (Scheme 1, path B). Finally, indenone **4a** can derive directly from **5a**. Indeed, under the experimental conditions (*i.e.*, high temperature and excess of Et_3N), diketone (**III**) can be deprotonated and the obtained carbanion can attack the -CN functionality forming the cycle. Finally, after protonation (for example, by Et_3NH^+) and subsequent imine-enamine rearrangement of (**IV**), **4a** product is formed. A confirmation of the above mechanism was given by treating **5a** under the cyclocarbonylative Sonogashira conditions of Table 1, entry 1 (0.4 mol% of $\text{PdCl}_2(\text{PPh}_3)_2$, CH_2Cl_2 and Et_3N , 20 atm of CO, 100 °C, for 4h). Indeed, indenone **4a** was exclusively formed (Scheme S2 in Supporting Information). In order to obtain more information regarding the reactivity of benzamide **1**, further experiments were performed under different experimental conditions.



Scheme 1. Plausible mechanism for the formation of products **3a**, **4a** and **5a** via Sonogashira cyclocarbonylative reaction between 2-ethynylbenzamide **1** and iodobenzene **2a**.

As reported in Table 1, the nature of the solvents seemed to influence markedly the chemoselectivity of the reactions. In fact, when CH₂Cl₂ is used as solvent the chemoselectivity depends on the experimental conditions (Table 1, entries 1-5). On the contrary, tests carried out in THF (Table 1, entries 6-8) afforded **5a** with high selectivity (71-79%), regardless of temperature and duration of the reactions. The particular behavior of THF can be ascribed to a strong coordination effect (hydrogen bond) between ketoenol hydrogen and THF oxygen atom as depicted in Figure 2.

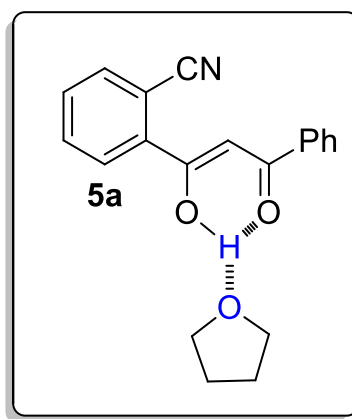
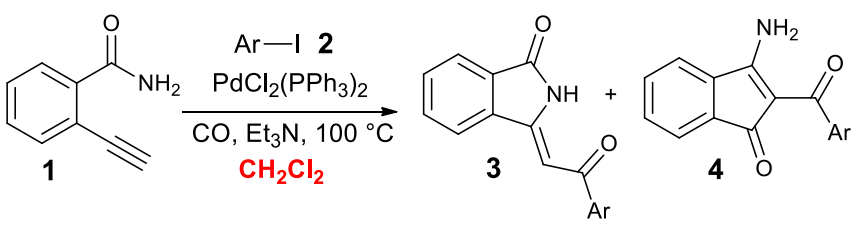


Figure 2. Stabilization of (Z)-2-(1-hydroxy-3-oxo-3-phenylprop-1-en-1-yl)benzonitrile (**5a**) by coordination with THF.

As for as acetonitrile and DMF are concerned, in the first case the preferential formation of **5a** was observed at high temperature (Table 1, entry 9) while the use of DMF involved the formation of a mixture of products.

Given the data obtained in the reactions between 2-ethynylbenzamide **1** and iodobenzene **2a**, the extension of Sonogashira cyclocarbonylative reactions to iodoarenes having different steric and electronic requirements was subsequently investigated. The reactions were carried out under the reaction conditions which provided the desired isoindolinone **3a** with better conversion and chemoselectivity, *i.e.* operating in dichloromethane and triethylamine, with 0.4 mol% of $\text{PdCl}_2(\text{PPh}_3)_2$, 20 atm of CO, at 100 ° C. Main results are described in Table 2. In all cases a mixture of isoindolinone **3** and indenone **4** was obtained. However the products could be easily separated, and isolated chemically pure with satisfactory yields. As reported in Table 2, compared to preliminary reactions conducted with iodobenzene **2a**, the use of *p*-methoxy derivative **2b** showed a similar trend in terms of chemoselectivity and yield. Moreover, increasing the reaction time, an increase in the conversion was observed while the ratio between **3b** and **4b** remained substantially the same (Table 2, entries 2-4). Instead, when the reaction was performed with the more sterically hindered *ortho*-methoxyiodobenzene **2c**, a decrease in reaction rate was observed even if the reaction was carried out with 1 mol% of $\text{PdCl}_2(\text{PPh}_3)_2$ (Table 2, entry 5, 73% conversion). Finally the reaction could be performed successfully also in the case of iodoarenes characterized by electron-withdrawing groups such as -Cl and -CN (**2d-e**) (Table 2, entries

6-7).

Table 2. Cyclocarbonylative Sonogashira reactions of 2-ethynylbenzamide **1** with iodoarenes **2** performed in CH₂Cl₂.


Entry ^a	Ar	2	t (h)	Conversion ^b (%)	3,4	Selectivity ^c (%)	
						3	4
1	Ph	a	4	80	a	57 (34)	43 (21)
2	4-OMePh	b	4	79	b	55 (38)	45 (30)
3	4-OMePh	b	8	84	b	56	44
4	4-OMePh	b	24	100	b	58	42
5 ^d	2-OMePh	c	24	73	c	50 (37)	50 (29)
6	4-ClPh	d	4	90	d	58 (32)	42 (37)
7	4-CNPh	e	4	86	e	36 (15)	64 (44)

a) All reactions were carried with 2-ethynylbenzamide **1** (1.0 mmol), iodoarene **2** (1.0 mmol), CO (20 atm), PdCl₂(PPh₃)₂ (0.4 mol%), Et₃N (1.5 mL) and CH₂Cl₂ (4.0 mL) at 100 °C, unless otherwise stated. **b)** Conversion was determined by ¹H-NMR peak integration on the crude product. **c)** Selectivity was estimated by ¹H-NMR spectroscopy; isolated yields of pure products are reported in parentheses. **d)** Reaction performed with 1 mol% of PdCl₂(PPh₃)₂.

Considering the interesting synthetic potentialities of compound **5a** possessing a diketo group⁶⁰⁻⁶⁶ in keto-enolic form, a few cyclocarbonylative Sonogashira reactions between 2-ethynylbenzamide **1** and different iodoarenes **2** were also performed in THF. As reported in Table 3, a high conversion of the reactants (75-100%) was observed and the formation of a mixture of isoindolinone **3** and ketoenol **5** was obtained. Nevertheless, compounds **5a-e** could be easily isolated chemically pure in moderate yields. The composition of crude products depended on the nature of the functional group on iodoarene **2**. Indeed, using 4-iodoanisole **2b** we obtained almost the same result of iodobenzene **2a** (Table 3,

entries 1-2), while in the reaction between **1** and 1-chloro-4-iodobenzene **2c** (Table 3 entry 3) the selectivity changed slightly (40/60).

Table 3. Cyclocarbonylative Sonogashira reactions of 2-ethynylbenzamide **1** with iodoarenes **2** performed in THF.

Entry ^a	Ar	2	t (h)	Conversion ^b (%)	3,5	Selectivity ^c (%)	
						3	5
1	Ph	a	4	94	a	29	71 (44)
2	4-OMePh	b	4	75	b	29	71 (41)
3	4-ClPh	d	4	89	d	40	60 (39)
4	4-CNPh	e	4	100	e	72	28 (22)

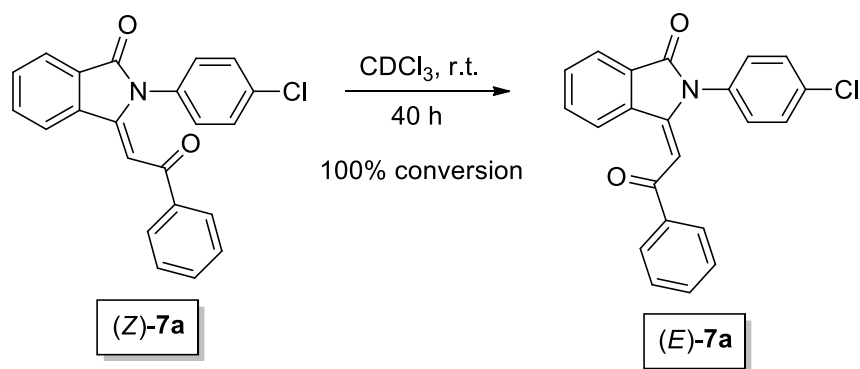
a) All reactions were carried with 2-ethynylbenzamide **1** (1.0 mmol), iodoarene **2** (1.0 mmol), CO (20 atm), PdCl₂(PPh₃)₂ (0.4 mol%), Et₃N (1.5 mL) and CH₂Cl₂ (4.0 mL) at 100 °C, unless otherwise stated. **b)** Conversion was determined by ¹H-NMR peak integration on the crude product. **c)** Selectivity was estimated by ¹H-NMR spectroscopy; isolated yields of pure products are reported in parentheses.

Finally, using 4-iodobenzonitrile **2e** as reactant, there was a clear prevalence of the isoindolinone **3e** (72%) (Table 3, entry 4). These data clearly showed the need for a fine-tuning of the cyclocarbonylation process in the event that keto-enols **5** possessing strong electron withdrawing groups are desired.

The obtained results described so far indicated that the free -NH₂ group is involved in the formation of different products depending on the experimental conditions used. In order to increase the chemoselectivity towards isoindolinones compounds, *N*-(4-chlorophenyl)-2-ethynylbenzamide **6** was prepared from 2-iodobenzoic acid according to the four-step synthetic procedure depicted in the Scheme S3 of Supporting Information.

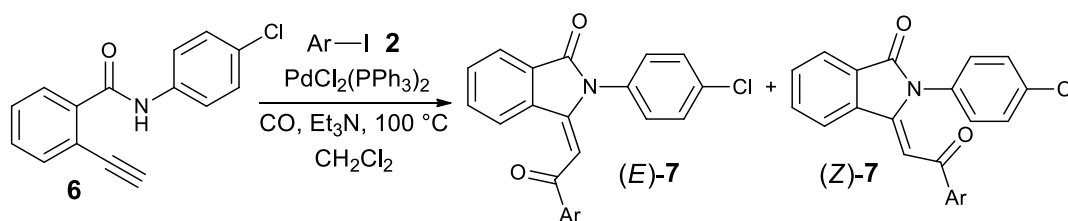
Initially, *N*-(4-chlorophenyl)-2-ethynylbenzamide **6** was submitted to a Sonogashira

cyclocarbonylation reaction with iodobenzene **2a** under experimental conditions which generally favored isoindolinone formation, *i.e.* CH₂Cl₂, 100 °C, 20 atm CO, 0.4 mol % of PdCl₂(PPh₃)₂ (Table 4, entry 1). To our delight, analysis of crude product indicated the complete conversion of starting materials and the formation of two isomers which were identified as (*Z*)- and (*E*)-2-(4-chlorophenyl)-3-(2-oxo-2-phenylethylidene)isoindolin-1-one **7a**. Moreover the synthesis was highly stereoselective, *i.e.* with a (*E*)-**7a**/*(Z)*-**7a** molar ratio of 89/11, probably due to the lower steric hindrance of the (*E*)-isomer. Indeed, when a sample of (*Z*)-**7a** in CDCl₃ was maintained for 40 h at room temperature, its complete conversion into (*E*)-isomer was observed (Scheme 2). As previously observed,⁴⁸ the presence of acid traces in chloroform could cause the interconversion to occur.



Scheme 2. Interconversion of 2-(4-chlorophenyl)-3-(2-oxo-2-phenylethylidene)isoindolin-1-one **7a** from the (*Z*)-isomer to the (*E*)-isomer, performed in CDCl₃ at room temperature.

When the cyclocarbonylative reaction of amide **6** with iodobenzene **2a** was carried out for a longer reaction time (24 h) but at 50 °C, a reduction of conversion was observed (84%) while stereoselectivity resulted almost the same (Table 4, entry 2, (*E*)-**7a**/*(Z)*-**7a** molar ratio 90/10). Therefore all subsequent reactions were carried out at 100 °C for 4 h (Table 4, entries 3-9). In all cases a quantitative conversion of reagents was observed and a generally a mixture of two E/Z isomers (ca. 90/10) was obtained. Both compounds could be easily separated and isolated chemically pure by neutral alumina column chromatography.

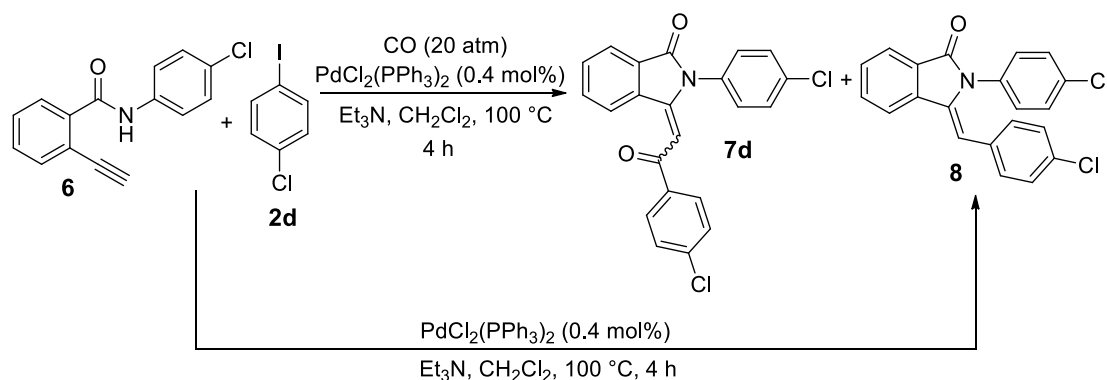
Table 4. Cyclocarbonylative Sonogashira reactions of *N*-(4-chlorophenyl)-2-ethynylbenzamide **6** with iodoarenes **2**.

Entry ^a	Ar	2	t (h)	Conversion ^b (%)	7	Selectivity ^c (%)	
						<i>(E)</i> -7	<i>(Z)</i> -7
1	Ph	a	4	100	a	89 (66)	11 (6)
2 ^d	Ph	a	24	84	a	90	10
3	4-OMePh	b	4	100	b	88 (69)	12 (10)
4	2-OMePh	c	4	100	c	93 (74)	7 (3)
5	4-ClPh	d	4	100	d	84 ^f (51)	10 ^f (7)
6 ^e	4-ClPh	d	4	100	d	86 ^f	10 ^f
7	1-Napht	f	4	100	f	89 (69)	11 (5)
8	4-MePh	g	4	100	g	90 (67)	10 (7)
9	2-MePh	h	4	100	h	88 (60)	12 (5)

a) All reactions were carried with *N*-(4-chlorophenyl)-2-ethynylbenzamide **6** (1.0 mmol), iodoarene **2** (1.0 mmol), CO (20 atm), $\text{PdCl}_2(\text{PPh}_3)_2$ (0.4 mol%), Et_3N (1.5 mL) and CH_2Cl_2 (4.0 mL) at $100\text{ }^\circ\text{C}$, unless otherwise stated. **b)** Conversion was determined by $^1\text{H-NMR}$ peak integration on the crude product. **c)** Selectivity was estimated by $^1\text{H-NMR}$ spectroscopy; isolated yields of pure products are reported in parentheses. **d)** Reaction performed at $50\text{ }^\circ\text{C}$. **e)** Reaction performed under 40 atm of CO. **f)** The remainder of the product was *(Z)*-3-(4-chlorobenzylidene)-2-(4-chlorophenyl)isoindolin-1-one **8**.

Reactions performed between amide **6** and iodoarenes possessing electron donating groups (*i.e.*, **2b-c** and **2f-h**) (Table 4, entries 3-4 and 7-9) afforded the *(E)*-isomers as principle products in good yields (60-74%). In the case of cross coupling with 1-chloro-4-iodobenzene **2d** (Table 4, entry 5), a small amount of *(Z)*-3-(4-chlorobenzylidene)-2-(4-chlorophenyl)isoindolin-1-one **8** was obtained. Its structure has been assigned by comparison with a pure sample prepared via cyclic Sonogashira reaction

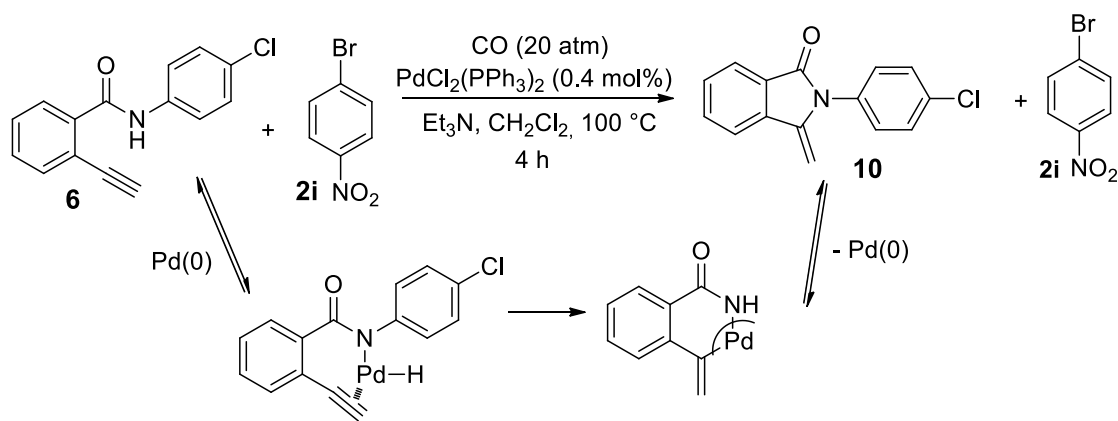
as depicted in Scheme 3. The products composition did not change even performing the cyclocarbonylative reaction of amide **6** with 1-chloro-4-iodobenzene **2d** under 40 atm of carbon monoxide pressure (Table 4, entry 6).



Scheme 3. Cyclocarbonylative Sonogashira and cyclic Sonogashira reactions of amide **6** with 1-chloro-4-iodobenzene **2d**.

A cyclocarbonylative Sonogashira reaction of *N*-(4-chlorophenyl)-2-ethynylbenzamide **6** was also carried out in the presence of the electron-poor 4-iodobenzonitrile **2e**: in this case, only small amounts of (*E*)-4-(2-(2-(4-chlorophenyl)-3-oxoisindolin-1-ylidene)acetyl)benzonitrile (*E*)-**7e** (yield 18%) and (*Z*)-4-(2-(2-(4-chlorophenyl)-3-oxoisindolin-1-ylidene)acetyl)benzonitrile (*Z*)-**7e** (yield 5%), together with (*Z*)-4-((2-(4-chlorophenyl)-3-oxoisindolin-1-ylidene)methyl)benzonitrile **9** (yield 4%) were isolated (Scheme S4 in Supporting Information).

Finally, considering the general toxicity of iodoarenes, a test between 4-bromonitrobenzene **2i** and ethynylbenzamide **6** was performed under 20 atm of CO, at 100 °C for 4 h (Scheme 4). Unfortunately, the bromoderivative **2i** was recovered unreacted while benzamide **6** was completely consumed. After purification of the crude mixture, 2-(4-chlorophenyl)-3-methyleneisindolin-1-one (**10**)⁴⁵ was isolated in 85% yield. The formation of cyclisation product **10** could be explained considering the insertion of Pd(0) into N-H bond, Pd-hydride addition to the triple bond followed by reductive elimination with generation of methyleneisindolinone **10** and Pd(0).



Scheme 4. Cyclocarbonylative Sonogashira and cyclic Sonogashira reactions of amide **6** with 1-chloro-4-iodobenzene **2d**.

CONCLUSIONS

In conclusion, we have developed an atom-efficient approach to alkylidene isoindolin-1-ones through a Pd-catalysed copper-free cyclocarbonylative Sonogashira reaction between benzamides and aryl iodides. In particular, when 2-ethynylbenzamide **1** was used in CH₂Cl₂, the reaction generally afforded (*Z*)-isoindolinones in major amount together with indenones derivatives. Changing the solvent to THF determined the preferential formation of keto-enols compounds. On the other hand, the Sonogashira cyclocarbonilative reaction of *N*-(4-chlorophenyl)-2-ethynylbenzamide **6** with iodoarenes generated almost exclusively the corresponding (*E*)-isoindolinones in satisfactory yields.

EXPERIMENTAL SECTION

General information. Solvents were purified by conventional methods, distilled and stored over activated molecular sieves under argon. All the chemicals were purchased from commercial sources and used as received without purification. All the operations under inert atmosphere were carried out using standard Schlenk techniques and employing dried nitrogen. Reactions that required heating were performed in an oil bath. For all reactions, conversion was monitored by thin-layer chromatography (TLC) analysis on pre-coated silica gel plates (VWR Macherey-Nagel, 0.2 mm thick) or pre-coated neutral alumina plates (Sigma Aldrich, 0.25 mm thick). Column chromatography was performed with

Fluka silica gel, pore size 60 Å, 70-230 mesh, 63-200 µm or Sigma Aldrich activated, neutral alumina. ¹H-NMR and ¹³C-NMR spectra were recorded at room temperature in CDCl₃ or DMSO-*d*₆ solution with a Varian INOVA – 600 spectrometer, operating at a frequency of 600 MHz for ¹H and 150 MHz for ¹³C, using the residual solvent peak as internal reference; chemical shifts (δ) values are given in parts per million (ppm) and coupling constants (*J*) in Hertz. Mass spectra were obtained with an Applied Biosystems-MDS Sciex API 4000 triple quadrupole mass spectrometer (Concord, Ont., Canada), equipped with a Turbo-V ion-spray (TIS) source. Elemental analyses were performed on a Elementar Vario Micro Cube CHN-analyzer.

Synthesis of ethynylbenzamides. 2-((Trimethylsilyl)ethynyl)benzamide (**B**).⁶⁷ 2-Bromobenzamide (**A**) (7.00 g, 35.0 mmol), PdCl₂(PPh₃)₂ (983 mg, 1.40 mmol), CuI (267 mg, 1.40 mmol), Et₃N (160 mL) and DMF (50 mL) were mixed together, then trimethylsilylacetylene (7.4 mL, 52.5 mmol) was added dropwise. The resulting mixture was refluxed under stirring for 24 h, then it was cooled to room temperature, hydrolyzed with saturated ammonium chloride solution (150 mL) and extracted with CH₂Cl₂ (3×150 mL). The combined organic phases were washed with brine (150 mL), dried over anhydrous Na₂SO₄ and the solvent was removed under vacuum. The crude product was purified by column chromatography (SiO₂, *n*-hexane/AcOEt 1:1) to give 3.18 g (yield 42%) of 2-((trimethylsilyl)ethynyl)benzamide (**B**).⁶⁷

¹H-NMR (600 MHz, CDCl₃), δ (ppm): 0.28 (9H, s); 6.04 (1H, bs); 7.43-7.46 (2H, m); 7.55-7.56 (1H, m); 7.76 (1H, bs); 8.13-8.17 (1H, m). ¹³C-NMR (150 MHz, CDCl₃), δ (ppm): -0.2 (3C); 102.3; 104.4; 120.1; 129.3; 130.6; 131.1; 134.1; 134.7; 168.2. LC-MS (APCI⁺), *m/z*: 218.1 [M+H]⁺.

2-Ethynylbenzamide (**I**).⁶⁷ 2-((Trimethylsilyl)ethynyl)benzamide (**B**) (3.18 g, 14.6 mmol), cesium fluoride (3.33 g, 21.9 mmol) and methanol (100 mL) were mixed together. The resulting mixture was left under stirring for 3 h at room temperature, then it was hydrolyzed with brine (100 mL) and extracted with AcOEt (3×50 mL). The combined organic phases were washed with brine (100 mL), dried over anhydrous Na₂SO₄ and the solvent was removed under vacuum. The crude product was purified by

column chromatography (SiO₂, *n*-hexane/AcOEt 1:1) to give 1.51 g (yield 71%) of 2-ethynylbenzamide (**1**).⁶⁷

¹H-NMR (600 MHz, CDCl₃), δ (ppm): 3.52 (1H, s); 6.10 (1H, bs); 7.34 (1H, bs); 7.45-7.49 (2H, m); 7.59-7.61 (1H, m); 8.08-8.09 (1H, m). ¹³C-NMR (150 MHz, CDCl₃), δ (ppm): 82.5; 84.2; 119.1; 129.6; 130.3; 131.2; 134.5; 135.5; 168.3. LC-MS (APCI⁺), *m/z*: 146.1 [M+H]⁺.

2-Iodobenzoyl chloride (**D**).⁶⁸ 2-Iodobenzoic acid (**C**) (4.97 g, 20.0 mmol), DMF (46 μL, 0.6 mmol) and CH₂Cl₂ (50 mL) were mixed together, then oxalyl chloride (3.5 mL, 40.8 mmol), was added dropwise to the solution at 0 °C. The mixture was left under stirring for 2 h at room temperature, then it was evaporated under vacuum to give 2-iodobenzoyl chloride (**D**)⁶⁸ (4.66 g, yield 87%) which was used without further purification.

¹H-NMR (600 MHz, CDCl₃), δ (ppm): 7.23-7.26 (1H, m); 7.49-7.51 (1H, m); 8.04-8.05 (1H, m); 8.07-8.08 (1H, m). ¹³C-NMR (150 MHz, CDCl₃), δ (ppm): 94.1; 128.2; 133.9; 134.3; 138.2; 141.7; 166.8.

N-(4-Chlorophenyl)-2-iodobenzamide (**E**).⁶⁹ 4-Chloroaniline (3.19 g, 25.0 mmol), Et₃N (3.5 mL, 25.0 mmol) and CH₂Cl₂ (25 mL) were mixed together, then a solution of 2-iodobenzoyl chloride (**D**) (6.67 g, 25.0 mmol) in CH₂Cl₂ (25 mL) was added dropwise to the solution at 0 °C. The mixture was left under stirring for 90 min at room temperature, then it was hydrolyzed with water (100 mL) and extracted with CH₂Cl₂ (3×50 mL). The combined organic phases were washed, in order, with HCl 1 M solution (100 mL), water (100 mL), saturated NaHCO₃ solution (100 mL) and brine (100 mL), then dried over anhydrous Na₂SO₄ and the solvent was removed under vacuum to give *N*-(4-chlorophenyl)-2-iodobenzamide (**E**)⁶⁹ (7.24 g, yield 81%) which was used without further purification.

¹H-NMR (600 MHz, CDCl₃), δ (ppm): 7.13-7.15 (1H, m); 7.32 (2H, d, *J* = 8.7 Hz); 7.39-7.42 (1H, m); 7.46-7.48 (1H, m); 7.57 (2H, d, *J* = 8.7 Hz); 7.70 (1H, bs); 7.88-7.89 (1H, m). ¹³C-NMR (150 MHz, CDCl₃), δ (ppm): 92.4; 121.4 (2C); 128.2; 128.4; 129.0 (2C); 129.8; 131.5; 136.1; 139.9; 141.6; 167.4. LC-MS (APCI⁺), *m/z*: 358.0 [M+H]⁺.

N-(4-Chlorophenyl)-2-((trimethylsilyl)ethynyl)benzamide (**F**).⁷⁰ *N*-(4-Chlorophenyl)-2-iodobenzamide (**E**) (6.80 g, 19.0 mmol), PdCl₂(PPh₃)₂ (534 mg, 0.76 mmol), CuI (145 mg, 0.76 mmol), Et₃N (5.3 mL,

38.0 mmol) and THF (120 mL) were mixed together, then trimethylsilylacetylene (4.1 mL, 28.9 mmol) was added dropwise. The resulting mixture was left under stirring for 24 h at room temperature, then it was hydrolyzed with saturated ammonium chloride solution (100 mL) and extracted with CH₂Cl₂ (3×100 mL). The combined organic phases were washed with brine (100 mL), dried over anhydrous Na₂SO₄ and the solvent was removed under vacuum. The crude product was purified by column chromatography (SiO₂, *n*-hexane/AcOEt 6:1) to give 4.95 g (yield 79%) of *N*-(4-chlorophenyl)-2-((trimethylsilyl)ethynyl)benzamide (**F**).⁷⁰

¹H-NMR (600 MHz, CDCl₃), δ (ppm): 0.25 (9H, s); 7.34 (2H, d, *J* = 9.0 Hz); 7.44-7.48 (2H, m); 7.58-7.59 (1H, m); 7.62 (2H, d, *J* = 9.0 Hz); 8.10-8.12 (1H, m); 9.33 (1H, bs). ¹³C-NMR (150 MHz, CDCl₃), δ (ppm): -0.2 (3C); 102.9; 103.0; 119.3; 121.3 (2C); 129.0 (2C); 129.4; 129.5; 130.3; 130.9; 134.1; 135.4; 136.5; 164.0. LC-MS (APCI⁺), *m/z*: 328.1 [M+H]⁺.

N-(4-Chlorophenyl)-2-ethynylbenzamide (**6**). *N*-(4-Chlorophenyl)-2-((trimethylsilyl)ethynyl)benzamide (**F**) (3.94 g, 12.0 mmol) and methanol (100 mL) were mixed together, then a solution of tetrabutylammonium fluoride trihydrate (4.54 g, 14.4 mmol) in methanol (100 mL) was added dropwise to the solution. The resulting mixture was left under stirring for 1 h at room temperature, then it was hydrolyzed with brine (200 mL) and extracted with AcOEt (3×150 mL). The combined organic phases were washed with brine (100 mL), dried over anhydrous Na₂SO₄ and the solvent was removed under vacuum. The crude product was purified by column chromatography (SiO₂, *n*-hexane/AcOEt 4:1) to give 1.78 g (yield 58%) of *N*-(4-chlorophenyl)-2-ethynylbenzamide (**6**).

¹H-NMR (600 MHz, CDCl₃), δ (ppm): 3.57 (1H, s); 7.27 (2H, d, *J* = 9.0 Hz); 7.39-7.42 (2H, m); 7.54-7.56 (1H, m); 7.59 (2H, d, *J* = 9.0 Hz); 7.91-7.92 (1H, m); 9.10 (1H, bs). ¹³C-NMR (150 MHz, CDCl₃), δ (ppm): 81.9; 84.4; 118.4; 121.2 (2C); 129.0 (2C); 129.5; 129.6; 129.9; 130.9; 134.2; 136.4; 136.5; 164.3. LC-MS (APCI⁺), *m/z*: 256.0 [M+H]⁺. Anal. calcd for C₁₅H₁₀ClNO: C, 70.46; H, 3.94; N, 5.48; found: C, 70.39; H, 3.99; N, 5.47.

Cyclocarbonylative Sonogashira reactions of 2-ethynylbenzamide (1). *General procedure.* A Pyrex

Schlenk tube under CO atmosphere was charged with 2-ethynylbenzamide (**1**) (1.0 mmol), iodoarene (1.0 mmol), Et₃N (1.5 mL) and the solvent (4.0 mL). This solution was introduced by a steel siphon into a 25 mL stainless steel autoclave, fitted with a Teflon inner crucible and a stirring bar, previously carried with PdCl₂(PPh₃)₂ (0.4-1.0 mol%) and placed under vacuum (0.1 Torr). The reactor was pressurized with CO (20 atm) and the mixture was stirred for a selected time at a selected temperature. After removal of excess CO (fume hood), the reaction mixture was diluted with CH₂Cl₂ (20 mL), washed with brine (15 mL), dried over anhydrous Na₂SO₄ and the solvent was removed under vacuum. The reagent conversion and the product composition were determined by ¹H-NMR spectroscopic analysis. All crude products were purified through column chromatography on silica gel and characterized with ¹H-NMR, ¹³C-NMR, LC-MS and elemental analysis techniques.

Cyclocarbonylative Sonogashira of 2-ethynylbenzamide (1) and iodobenzene (2a) in CH₂Cl₂ at 100 °C (Table 1, entry 1 & Table 2, entry 1). Following the general procedure, 2.8 mg (0.004 mmol) of PdCl₂(PPh₃)₂, 145.2 mg (1.0 mmol) of 2-ethynylbenzamide (**1**), 204.0 mg (1.0 mmol) of iodobenzene (**2a**), 1.5 mL of Et₃N and 4 mL of CH₂Cl₂ were put in the autoclave. The resulting mixture was stirred for 4 h at 100 °C. The crude product was purified through column chromatography (SiO₂, *n*-hexane/AcOEt 1:1), obtaining 85 mg (yield 34%) of (*Z*)-3-(2-oxo-2-phenylethylidene)isoindolin-1-one (**3a**) and 52 mg (yield 21%) of 3-amino-2-benzoyl-1*H*-inden-1-one (**4a**).

3a. ¹H-NMR (600 MHz, DMSO-*d*₆), δ (ppm): 7.41 (1H, s); 7.58-7.61 (2H, m); 7.67-7.70 (1H, m); 7.72-7.74 (1H, m); 7.81-7.83 (1H, m); 7.85-7.86 (1H, m); 8.20-8.21 (2H, m); 8.35-8.37 (1H, m); 10.92 (1H, bs). ¹³C-NMR (150 MHz, DMSO-*d*₆), δ (ppm): 95.7; 122.6; 123.4; 128.1 (2C); 128.5; 128.8 (2C); 132.1; 133.1; 133.2; 137.2; 137.8; 147.6; 168.8; 189.8. LC-MS (APCI⁺), *m/z*: 250.1 [M+H]⁺. Anal. calcd for C₁₆H₁₁NO₂: C, 77.10; H, 4.45; N, 5.62; found: C, 77.19; H, 4.41; N, 5.63.

4a. ¹H-NMR (600 MHz, DMSO-*d*₆), δ (ppm): 7.39-7.42 (2H, m); 7.47-7.51 (2H, m); 7.60-7.62 (2H, m); 7.63-7.67 (2H, m); 8.06-8.10 (1H, m); 10.09 (1H, bs); 10.21 (1H, bs). ¹³C-NMR (150 MHz, DMSO-*d*₆), δ (ppm): 103.0; 121.4; 121.5; 127.2 (2C); 128.5 (2C); 130.5; 132.3; 133.5; 134.9; 135.5; 140.1; 172.2; 186.7; 190.2. LC-MS (APCI⁺), *m/z*: 250.1 [M+H]⁺. Anal. calcd for C₁₆H₁₁NO₂: C, 77.10; H,

4.45; N, 5.62; found: C, 77.17; H, 4.37; N, 5.61.

Cyclocarbonylative Sonogashira of 2-ethynylbenzamide (1) and iodobenzene (2a) in CH₂Cl₂ at 50 °C (Table 1, entry 5). Following the general procedure, 2.8 mg (0.004 mmol) of PdCl₂(PPh₃)₂, 145.2 mg (1.0 mmol) of 2-ethynylbenzamide (**1**), 204.0 mg (1.0 mmol) of iodobenzene (**2a**), 1.5 mL of Et₃N and 4 mL of CH₂Cl₂ were put in the autoclave. The resulting mixture was stirred for 24 h at 50 °C. The crude product was purified through column chromatography (SiO₂, CH₂Cl₂), obtaining 105 mg (yield 42%) of (Z)-2-(1-hydroxy-3-oxo-3-phenylprop-1-en-1-yl)benzonitrile (**5a**).

5a. ¹H-NMR (600 MHz, CDCl₃), δ (ppm): 6.95 (1H, s); 7.48-7.51 (2H, m); 7.56-7.59 (1H, m); 7.61-7.64 (1H, m); 7.71-7.74 (1H, m); 7.82-7.83 (1H, m); 7.97-8.01 (3H, m); 16.44 (1 H, bs). ¹³C-NMR (150 MHz, CDCl₃), δ (ppm): 96.0; 110.6; 118.0; 127.4 (2C); 128.8 (2C); 129.0; 131.5; 132.8; 133.0; 134.7; 134.7; 139.1; 183.1; 186.2. LC-MS (APCI⁺), *m/z*: 250.1 [M+H]⁺. Anal. calcd for C₁₆H₁₁NO₂: C, 77.10; H, 4.45; N, 5.62; found: C, 77.18; H, 4.39; N, 5.61.

Cyclocarbonylative Sonogashira of 2-ethynylbenzamide (1) and iodobenzene (2a) in THF at 100 °C (Table 1, entry 6 & Table 3, entry 1). Following the general procedure, 2.8 mg (0.004 mmol) of PdCl₂(PPh₃)₂, 145.2 mg (1.0 mmol) of 2-ethynylbenzamide (**1**), 204.0 mg (1.0 mmol) of iodobenzene (**2a**), 1.5 mL of Et₃N and 4 mL of THF were put in the autoclave. The resulting mixture was stirred for 4 h at 100 °C. The crude product was purified through column chromatography (SiO₂, CH₂Cl₂), obtaining 110 mg (yield 44%) of (Z)-2-(1-hydroxy-3-oxo-3-phenylprop-1-en-1-yl) benzonitrile (**5a**).

Cyclocarbonylative Sonogashira of 2-ethynylbenzamide (1) and iodobenzene (2a) in acetonitrile at 100 °C (Table 1, entry 9). Following the general procedure, 2.8 mg (0.004 mmol) of PdCl₂(PPh₃)₂, 145.2 mg (1.0 mmol) of 2-ethynylbenzamide (**1**), 204.0 mg (1.0 mmol) of iodobenzene (**2a**), 1.5 mL of Et₃N and 4 mL of acetonitrile were put in the autoclave. The resulting mixture was stirred for 4 h at 100 °C. The composition of crude product was determined by ¹H-NMR analysis, resulting in a mixture of (Z)-3-(2-oxo-2-phenylethylidene) isoindolin-1-one (**3a**) and (Z)-2-(1-hydroxy-3-oxo-3-phenylprop-1-en-1-yl) benzonitrile (**5a**) in the molar ratio 78/22.

Cyclocarbonylative Sonogashira of 2-ethynylbenzamide (1) and iodobenzene (2a) in DMF at 100 °C

(Table 1, entry 11). Following the general procedure, 2.8 mg (0.004 mmol) of $\text{PdCl}_2(\text{PPh}_3)_2$, 145.2 mg (1.0 mmol) of 2-ethynylbenzamide (**1**), 204.0 mg (1.0 mmol) of iodobenzene (**2a**), 1.5 mL of Et_3N and 4 mL of DMF were put in the autoclave. The resulting mixture was stirred for 4 h at 100 °C. The composition of crude product was determined by ^1H -NMR analysis, resulting in a mixture of (Z)-3-(2-oxo-2-phenylethylidene)isoindolin-1-one (**3a**), 3-amino-2-benzoyl-1*H*-inden-1-one (**4a**) and (Z)-2-(1-hydroxy-3-oxo-3-phenylprop-1-en-1-yl) benzonitrile (**5a**) in the molar ratio 33/32/35.

Cyclocarbonylative Sonogashira of 2-ethynylbenzamide (1) and 4-iodoanisole (2b) in CH_2Cl_2 (Table 2, entry 2). Following the general procedure, 2.8 mg (0.004 mmol) of $\text{PdCl}_2(\text{PPh}_3)_2$, 145.2 mg (1.0 mmol) of 2-ethynylbenzamide (**1**), 234.0 mg (1.0 mmol) of 4-iodoanisole (**2b**), 1.5 mL of Et_3N and 4 mL of CH_2Cl_2 were put in the autoclave. The resulting mixture was stirred for 4 h at 100 °C. The crude product was purified through column chromatography (SiO_2 , *n*-hexane/ AcOEt 1:1), obtaining 106 mg (yield 38%) of (Z)-3-(2-(4-methoxyphenyl)-2-oxoethylidene)isoindolin-1-one (**3b**) and 84 mg (yield 30%) of 3-amino-2-(4-methoxybenzoyl)-1*H*-inden-1-one (**4b**).

3b. ^1H -NMR (600 MHz, CDCl_3), δ (ppm): 3.84 (3H, s); 6.79 (1H, s); 6.91-6.93 (2H, m); 7.56-7.58 (1H, m); 7.61-7.64 (1H, m); 7.77-7.78 (1H, m); 7.82-7.83 (1H, m); 7.96-7.99 (2H, m); 10.57 (1H, bs). ^{13}C -NMR (150 MHz, CDCl_3), δ (ppm): 55.5; 94.75; 113.9 (2C); 121.0; 124.0; 129.2; 130.2 (2C); 131.2; 131.7; 132.7; 137.1; 147.6; 163.5; 169.0; 189.4. LC-MS (APCI^+), m/z : 280.1 $[\text{M}+\text{H}]^+$. Anal. calcd for $\text{C}_{17}\text{H}_{13}\text{NO}_3$: C, 73.11; H, 4.69; N, 5.02; found: C, 73.07; H, 4.78; N, 5.02.

4b. ^1H -NMR (600 MHz, $\text{DMSO}-d_6$), δ (ppm): 3.82 (3H, s); 6.93-6.95 (2H, m); 7.49-7.51 (1H, m); 7.62-7.66 (4H, m); 8.02-8.05 (1H, m); 9.96 (1H, bs); 10.14 (1H, bs). ^{13}C -NMR (150 MHz, $\text{DMSO}-d_6$), δ (ppm): 55.3; 103.1; 112.5; 121.3; 121.3 (2C); 130.9 (2C); 132.2; 132.4; 133.4; 135.0; 135.5; 161.4; 172.2; 186.8; 189.18. LC-MS (APCI^+), m/z : 280.1 $[\text{M}+\text{H}]^+$. Anal. calcd for $\text{C}_{17}\text{H}_{13}\text{NO}_3$: C, 73.11; H, 4.69; N, 5.02; found: C, 73.05; H, 4.74; N, 5.01.

Cyclocarbonylative Sonogashira of 2-ethynylbenzamide (1) and 2-iodoanisole (2c) in CH_2Cl_2 (Table 2, entry 5). Following the general procedure, 7.1 mg (0.01 mmol) of $\text{PdCl}_2(\text{PPh}_3)_2$, 145.2 mg (1.0 mmol) of 2-ethynylbenzamide (**1**), 234.0 mg (1.0 mmol) of 2-iodoanisole (**2c**), 1.5 mL of Et_3N and 4 mL of

CH₂Cl₂ were put in the autoclave. The resulting mixture was stirred for 24 h at 100 °C. The crude product was purified through column chromatography (SiO₂, *n*-hexane/AcOEt 1:1), obtaining 104 mg (yield 37%) of (Z)-3-(2-(2-methoxyphenyl)-2-oxoethylidene)isoindolin-1-one (**3c**) and 81 mg (yield 29%) of 3-amino-2-(2-methoxybenzoyl)-1*H*-inden-1-one (**4c**).

3c. ¹H-NMR (600 MHz, CDCl₃), δ (ppm): 3.95 (3H, s); 6.94 (1H, s); 7.00-7.01 (1H, m); 7.03-7.06 (1H, m); 7.47-7.50 (1H, m); 7.58-7.64 (2H, m); 7.73-7.76 (2H, m); 7.87-7.88 (1H, m); 10.48 (1H, bs). ¹³C-NMR (150 MHz, CDCl₃), δ (ppm): 55.8; 100.2; 111.7; 120.9; 121.1; 123.5; 124.1; 130.6; 131.6; 132.7; 133.5; 135.9; 137.4; 146.5; 158.1; 169.1; 192.3. LC-MS (APCI⁺), *m/z*: 280.1 [M+H]⁺. Anal. calcd for C₁₇H₁₃NO₃: C, 73.11; H, 4.69; N, 5.02; found: C, 73.22; H, 4.63; N, 5.03.

4c. ¹H-NMR (600 MHz, DMSO-*d*₆), δ (ppm): 3.64 (3H, s); 6.91-6.93 (1H, m); 7.00-7.01 (1H, m); 7.08-7.10 (1H, m); 7.34-7.36 (1H, m); 7.40-7.42 (1H, m); 7.60-7.62 (2H, m); 8.03-8.04 (1H, m); 9.98 (1H, s); 10.06 (1H, s). ¹³C-NMR (150 MHz, DMSO-*d*₆), δ (ppm): 55.4; 104.5; 111.1; 119.7; 121.2; 121.6; 127.6; 130.0; 131.6; 132.3; 133.4; 135.1; 135.6; 156.4; 170.7; 186.6; 189.2. LC-MS (APCI⁺), *m/z*: 280.1 [M+H]⁺. Anal. calcd for C₁₇H₁₃NO₃: C, 73.11; H, 4.69; N, 5.02; found: C, 73.18; H, 4.64; N, 5.02.

Cyclocarbonylative Sonogashira of 2-ethynylbenzamide (1) and 1-chloro-4-iodobenzene (2d) in CH₂Cl₂ (Table 2, entry 6). Following the general procedure, 2.8 mg (0.004 mmol) of PdCl₂(PPh₃)₂, 145.2 mg (1.0 mmol) of 2-ethynylbenzamide (**1**), 238.5 mg (1.0 mmol) of 1-chloro-4-iodobenzene (**2d**), 1.5 mL of Et₃N and 4 mL of CH₂Cl₂ were put in the autoclave. The resulting mixture was stirred for 4 h at 100 °C. The crude product was purified through column chromatography (SiO₂, *n*-hexane/AcOEt 1:1), obtaining 91 mg (yield 32%) of (Z)-3-(2-(4-chlorophenyl)-2-oxoethylidene)isoindolin-1-one (**3d**) and 105 mg (yield 37%) of 3-amino-2-(4-chlorobenzoyl)-1*H*-inden-1-one (**4d**).

3d. ¹H-NMR (600 MHz, CDCl₃), δ (ppm): 6.81 (1H, s); 7.49 (2H, d, *J* = 8.7 Hz); 7.64-7.70 (2H, m); 7.82-7.83 (1H, m); 7.90-7.91 (1H, m); 7.98 (2H, d, *J* = 8.7 Hz); 10.57 (1H, bs). ¹³C-NMR (150 MHz, CDCl₃), δ (ppm): 94.2; 121.1; 124.3; 129.0 (2C); 129.3 (2C); 130.6; 132.1; 132.9; 136.7; 137.00; 139.4; 148.9; 169.00; 189.6. LC-MS (APCI⁺), *m/z*: 283.9 [M+H]⁺. Anal. calcd for C₁₆H₁₀ClNO₂: C, 67.74; H,

3.55; N, 4.94; found: C, 67.68; H, 3.61; N, 4.95.

4d. ¹H-NMR (600 MHz, DMSO-*d*₆), δ (ppm): 7.46 (2H, d, *J* = 8.4 Hz); 7.50-7.51 (1H, m); 7.61 (2H, d, *J* = 8.4 Hz); 7.64-7.66 (2H, m); 8.06-8.08 (1H, m); 10.14 (1H, bs); 10.19 (1H, bs). ¹³C-NMR (150 MHz, DMSO-*d*₆), δ (ppm): 102.9; 121.5; 121.7; 127.3 (2C); 130.4 (2C); 132.5; 133.8; 134.9; 135.2; 135.5; 138.8; 172.2; 186.8; 188.7. LC-MS (APCI⁺), *m/z*: 283.9 [M+H]⁺. Anal. calcd for C₁₆H₁₀ClNO₂: C, 67.74; H, 3.55; N, 4.94; found: C, 67.63; H, 3.59; N, 4.95.

Cyclocarbonylative Sonogashira of 2-ethynylbenzamide (1) and 4-iodobenzonitrile (2e) in CH₂Cl₂ (Table 2, entry 7). Following the general procedure, 2.8 mg (0.004 mmol) of PdCl₂(PPh₃)₂, 145.2 mg (1.0 mmol) of 2-ethynylbenzamide (**1**), 229.0 mg (1.0 mmol) of 4-iodobenzonitrile (**2e**), 1.5 mL of Et₃N and 4 mL of CH₂Cl₂ were put in the autoclave. The resulting mixture was stirred for 4 h at 100 °C. The crude product was purified through column chromatography (SiO₂, *n*-hexane/AcOEt 1:1), obtaining 41 mg (yield 15%) of (*Z*)-4-(2-(3-oxoisindolin-1-ylidene) acetyl)benzonitrile (**3e**) and 121 mg (yield 44%) of 4-(3-amino-1-oxo-1*H*-indene-2-carbonyl)benzonitrile (**4e**).

3e. ¹H-NMR (600 MHz, CDCl₃), δ (ppm): 6.81 (1H, s); 7.67-7.73 (2H, m); 7.82-7.85 (3H, m); 7.92-7.94 (1H, m); 8.12 (2H, d, *J* = 8.4 Hz); 10.56 (1H, bs). ¹³C-NMR (150 MHz, CDCl₃), δ (ppm): 93.8; 116.1; 117.9; 121.3; 124.4; 128.3 (2C); 132.4; 132.5 (2C); 132.8; 133.1; 136.8; 141.6; 150.0; 168.9; 189.3. LC-MS (APCI⁺), *m/z*: 275.1 [M+H]⁺. Anal. calcd for C₁₇H₁₀N₂O₂: C, 74.44; H, 3.67; N, 10.21; found: C, 74.52; H, 3.60; N, 10.22.

4e. ¹H-NMR (600 MHz, DMSO-*d*₆), δ (ppm): 7.50-7.52 (1H, m); 7.66-7.68 (2H, m); 7.70 (2H, d, *J* = 8.7 Hz); 7.87 (2H, d, *J* = 8.7 Hz); 8.09-8.11 (1H, m); 10.23 (1H, bs); 10.26 (1H, bs). ¹³C-NMR (150 MHz, DMSO-*d*₆), δ (ppm): 112.4; 118.7; 121.5; 121.9; 128.9 (2C); 131.4 (2C); 132.0; 132.6; 133.8; 134.8; 135.6; 144.3; 172.2; 186.7; 188.3. LC-MS (APCI⁺), *m/z*: 275.1 [M+H]⁺. Anal. calcd for C₁₇H₁₀N₂O₂: C, 74.44; H, 3.67; N, 10.21; found: C, 74.51; H, 3.59; N, 10.21.

Cyclocarbonylative Sonogashira of 2-ethynylbenzamide (1) and 4-iodoanisole (2b) in THF (Table 3, entry 2). Following the general procedure, 2.8 mg (0.004 mmol) of PdCl₂(PPh₃)₂, 145.2 mg (1.0 mmol) of 2-ethynylbenzamide (**1**), 234.0 mg (1.0 mmol) of 4-iodoanisole (**2b**), 1.5 mL of Et₃N and 4 mL of

THF were put in the autoclave. The resulting mixture was stirred for 4 h at 100 °C. The crude product was purified through column chromatography (SiO₂, CH₂Cl₂), obtaining 115 mg (yield 41%) of (Z)-2-(1-hydroxy-3-(4-methoxyphenyl)-3-oxoprop-1-en-1-yl) benzonitrile (**5b**).

5b. ¹H-NMR (600 MHz, CDCl₃), δ (ppm): 3.88 (3H, s); 6.91 (1H, s); 6.98 (2H, d, *J* = 9.0 Hz); 7.60 (1H, t); 7.71 (1H, t); 7.82 (1H, d, *J* = 7.8 Hz); 7.96-7.99 (3H, m); 16.59 (1H, bs). ¹³C-NMR (150 MHz, CDCl₃), δ (ppm): 55.5; 95.4; 110.4; 114.1 (2C); 118.1; 127.4; 128.9; 129.7 (2C); 131.2; 132.8; 134.7; 139.2; 163.7; 181.2; 186.5. LC-MS (APCI⁺), *m/z*: 280.1 [M+H]⁺. Anal. calcd for C₁₇H₁₃NO₃: C, 73.11; H, 4.69; N, 5.02; found: C, 73.21; H, 4.62; N, 5.03.

Cyclocarbonylative Sonogashira of 2-ethynylbenzamide (1) and 1-chloro-4-iodobenzene (2d) in THF (Table 3, entry 3). Following the general procedure, 2.8 mg (0.004 mmol) of PdCl₂(PPh₃)₂, 145.2 mg (1.0 mmol) of 2-ethynylbenzamide (**1**), 238.5 mg (1.0 mmol) of 1-chloro-4-iodobenzene (**2d**), 1.5 mL of Et₃N and 4 mL of THF were put in the autoclave. The resulting mixture was stirred for 4 h at 100 °C. The crude product was purified through column chromatography (SiO₂, CH₂Cl₂), obtaining 111 mg (yield 39%) of (Z)-2-(3-(4-chlorophenyl)-1-hydroxy-3-oxoprop-1-en-1-yl)benzonitrile (**5d**).

5d. ¹H-NMR (600 MHz, CDCl₃), δ (ppm): 6.93 (1H, s); 7.47 (2H, d, *J* = 8.4 Hz); 7.62-7.65 (1H, m); 7.72-7.75 (1H, m); 7.84 (1H, d, *J* = 7.8 Hz); 7.94 (2H, d, *J* = 8.4 Hz); 7.98 (1H, d, *J* = 7.8 Hz); 16.35 (1H, bs). ¹³C-NMR (150 MHz, CDCl₃), δ (ppm): 96.0; 110.6; 118.0; 128.8 (2C); 129.1; 129.2 (2C); 131.6; 132.8; 133.2; 134.8; 138.9; 139.4; 183.0; 185.1. LC-MS (APCI⁺), *m/z*: 284.1 [M+H]⁺. Anal. calcd for C₁₆H₁₀ClNO₂: C, 67.74; H, 3.55; N, 4.94; found: C, 67.82; H, 3.49; N, 4.93.

Cyclocarbonylative Sonogashira of 2-ethynylbenzamide (1) and 4-iodobenzonitrile (2e) in THF (Table 3, entry 4). Following the general procedure, 2.8 mg (0.004 mmol) of PdCl₂(PPh₃)₂, 145.2 mg (1.0 mmol) of 2-ethynylbenzamide (**1**), 229.0 mg (1.0 mmol) of 4-iodobenzonitrile (**2e**), 1.5 mL of Et₃N and 4 mL of THF were put in the autoclave. The resulting mixture was stirred for 4 h at 100 °C. The crude product was purified through column chromatography (SiO₂, CH₂Cl₂), obtaining 61 mg (yield 22%) of (Z)-2-(3-(4-cyanophenyl)-1-hydroxy-3-oxoprop-1-en-1-yl)benzonitrile (**5e**).

5e. ¹H-NMR (600 MHz, CDCl₃), δ (ppm): 7.00 (1H, s); 7.66-7.69 (1H, m); 7.75-7.77 (1H, m); 7.81

(2H, d, $J = 8.4$ Hz); 7.86-7.87 (1H, m); 8.01 (1H, d, $J = 7.8$ Hz); 8.09 (2H, d, $J = 8.4$ Hz); 16.16 (1H, bs). ^{13}C -NMR (150 MHz, CDCl_3), δ (ppm): 96.7; 110.6; 116.0; 117.9; 117.9; 127.8 (2C); 129.2; 132.0; 132.5 (2C); 132.9; 134.8; 138.5; 138.6; 182.9; 184.7. LC-MS (APCI⁺), m/z : 275.1 $[\text{M}+\text{H}]^+$. Anal. calcd for $\text{C}_{17}\text{H}_{10}\text{N}_2\text{O}_2$: C, 74.44; H, 3.67; N, 10.21; found: C, 74.55; H, 3.61; N, 10.21.

Cyclocarbonylative Sonogashira reactions of *N*-(4-chlorophenyl)-2-ethynylbenzamide (6). *General procedure.* A Pyrex Schlenk tube under CO atmosphere was charged with *N*-(4-chlorophenyl)-2-ethynylbenzamide (**6**) (1.0 mmol), haloarene (1.0 mmol), Et_3N (1.5 mL) and CH_2Cl_2 (4.0 mL). This solution was introduced by a steel siphon into a 25 mL stainless steel autoclave, fitted with a Teflon inner crucible and a stirring bar, previously carried with $\text{PdCl}_2(\text{PPh}_3)_2$ (0.4 mol%) and placed under vacuum (0.1 Torr). The reactor was pressurized with CO (20-40 atm) and the mixture was stirred for a selected time at a selected temperature. After removal of excess CO (fume hood), the reaction mixture was diluted with CH_2Cl_2 (20 mL), washed with brine (15 mL), dried over anhydrous Na_2SO_4 and the solvent was removed under vacuum. The reagent conversion and the product composition were determined by ^1H -NMR spectroscopic analysis. All crude products were purified through column chromatography on neutral alumina and characterized with ^1H -NMR, ^{13}C -NMR, LC-MS and elemental analysis techniques.

*Cyclocarbonylative Sonogashira of *N*-(4-chlorophenyl)-2-ethynylbenzamide (6) and iodobenzene (2a) at 100 °C (Table 4, entry 1).* Following the general procedure, 2.8 mg (0.004 mmol) of $\text{PdCl}_2(\text{PPh}_3)_2$, 255.7 mg (1.0 mmol) of *N*-(4-chlorophenyl)-2-ethynylbenzamide (**6**), 204.0 mg (1.0 mmol) of iodobenzene (**2a**), 1.5 mL of Et_3N and 4 mL of CH_2Cl_2 were put in the autoclave charged with 20 atm of CO. The resulting mixture was stirred for 4 h at 100 °C. The crude product was purified through column chromatography (neutral Al_2O_3 , *n*-hexane/ AcOEt 4:1), obtaining 238 mg (yield 66%) of (*E*)-2-(4-chlorophenyl)-3-(2-oxo-2-phenylethylidene)isoindolin-1-one ((*E*)-**7a**) and 22 mg (yield 6%) of (*Z*)-2-(4-chlorophenyl)-3-(2-oxo-2-phenylethylidene)isoindolin-1-one ((*Z*)-**7a**).

(*E*)-**7a**. ^1H -NMR (600 MHz, CDCl_3), δ (ppm): 6.53 (1H, s); 7.36 (2H, d, $J = 7.6$ Hz); 7.46 (2H, t, $J =$

7.8 Hz); 7.55-7.59 (3H, m); 7.67-7.69 (1H, m); 7.72-7.75 (1H, m); 7.84 (2H, d, $J = 7.6$ Hz); 7.97 (1H, d, $J = 7.2$ Hz); 8.94 (1H, d, $J = 7.8$ Hz). ^{13}C -NMR (150 MHz, CDCl_3), δ (ppm): 105.3; 123.6; 127.3; 128.1 (2C); 128.6 (2C); 129.4; 130.1 (4C); 131.9; 132.3; 132.9; 133.6; 133.8; 135.0; 138.8; 149.2; 166.8; 189.6. LC-MS (APCI $^+$), m/z : 360.1 $[\text{M}+\text{H}]^+$. Anal. calcd for $\text{C}_{22}\text{H}_{14}\text{ClNO}_2$: C, 73.44; H, 3.92; N, 3.89; found: C, 73.41; H, 3.98; N, 3.88.

(*Z*)-**7a**. ^1H -NMR (600 MHz, CDCl_3), δ (ppm): 6.61 (1H, s); 6.99 (2H, d, $J = 8.4$ Hz); 7.15 (2H, d, $J = 8.4$ Hz); 7.36-7.38 (2H, m); 7.49-7.52 (1H, m); 7.63-7.65 (2H, m); 7.68 (1H, d, $J = 7.8$ Hz); 7.73-7.76 (1H, m); 7.88 (1H, d, $J = 7.8$ Hz); 7.96 (1H, d, $J = 7.8$ Hz). ^{13}C -NMR (150 MHz, CDCl_3), δ (ppm): 101.6; 105.4; 120.3; 124.3; 128.3 (2C); 128.4 (2C); 128.5 (2C); 128.9 (2C); 130.1; 130.2; 131.2; 133.1; 133.2; 137.2; 138.0; 143.0; 167.5; 191.2. LC-MS (APCI $^+$), m/z : 360.1 $[\text{M}+\text{H}]^+$. Anal. calcd for $\text{C}_{22}\text{H}_{14}\text{ClNO}_2$: C, 73.44; H, 3.92; N, 3.89; found: C, 73.40; H, 3.99; N, 3.88.

Cyclocarbonylative Sonogashira of N-(4-chlorophenyl)-2-ethynylbenzamide (6) and iodobenzene (2a) at 50 °C (Table 4, entry 2). Following the general procedure, 2.8 mg (0.004 mmol) of $\text{PdCl}_2(\text{PPh}_3)_2$, 255.7 mg (1.0 mmol) of *N*-(4-chlorophenyl)-2-ethynylbenzamide (**6**), 204.0 mg (1.0 mmol) of iodobenzene (**2a**), 1.5 mL of Et_3N and 4 mL of CH_2Cl_2 were put in the autoclave charged with 20 atm of CO. The resulting mixture was stirred for 24 h at 50 °C. The composition of crude product was determined by ^1H -NMR analysis, resulting in a mixture of (*E*)-2-(4-chlorophenyl)-3-(2-oxo-2-phenylethylidene)isoindolin-1-one ((*E*)-**7a**) and (*Z*)-2-(4-chlorophenyl)-3-(2-oxo-2-phenylethylidene)isoindolin-1-one ((*Z*)-**7a**) in the molar ratio 90/10.

Cyclocarbonylative Sonogashira of N-(4-chlorophenyl)-2-ethynylbenzamide (6) and 4-iodoanisole (2b) (Table 4, entry 3). Following the general procedure, 2.8 mg (0.004 mmol) of $\text{PdCl}_2(\text{PPh}_3)_2$, 255.7 mg (1.0 mmol) of *N*-(4-chlorophenyl)-2-ethynylbenzamide (**6**), 234.0 mg (1.0 mmol) of 4-iodoanisole (**2b**), 1.5 mL of Et_3N and 4 mL of CH_2Cl_2 were put in the autoclave charged with 20 atm of CO. The resulting mixture was stirred for 4 h at 100 °C. The crude product was purified through column chromatography (neutral Al_2O_3 , *n*-hexane/AcOEt 3:1), obtaining 269 mg (yield 69%) of (*E*)-2-(4-chlorophenyl)-3-(2-(4-methoxyphenyl)-2-oxoethylidene)isoindolin-1-one ((*E*)-**7b**) and 39 mg (yield 10%) of (*Z*)-2-(4-

chlorophenyl)-3-(2-(4-methoxyphenyl)-2-oxoethylidene)isoindolin-1-one ((*Z*)-**7b**).

(*E*)-**7b**. ¹H-NMR (600 MHz, CDCl₃), δ (ppm): 3.85 (3H, s); 6.49 (1H, s); 6.91 (2H, d, *J* = 9.0 Hz); 7.36 (2H, d, *J* = 8.7 Hz); 7.56 (2H, d, *J* = 8.7 Hz); 7.63-7.65 (1H, m); 7.68-7.71 (1H, m); 7.83 (2H, d, *J* = 9.0 Hz); 7.94 (1H, d, *J* = 7.2 Hz); 8.86 (1H, d, *J* = 7.8 Hz). ¹³C-NMR (150 MHz, CDCl₃), δ (ppm): 55.5; 105.7; 113.8 (2C); 123.6; 127.38; 129.5; 130.1 (2C); 130.1 (2C); 130.6 (2C); 131.7; 131.7; 132.5; 133.6; 133.9; 135.0; 148.4; 163.5; 166.8; 188.3. LC-MS (APCI⁺), *m/z*: 390.1 [M+H]⁺. Anal. calcd for C₂₃H₁₆ClNO₃: C, 70.86; H, 4.14; N, 3.59; found: C, 70.75; H, 4.21; N, 3.59.

(*Z*)-**7b**. ¹H-NMR (600 MHz, CDCl₃), δ (ppm): 3.86 (3H, s); 6.58 (1H, s); 6.84 (2H, d, *J* = 9.0 Hz); 7.00 (2H, d, *J* = 8.7 Hz); 7.15 (2H, d, *J* = 8.7 Hz); 7.62 (2H, d, *J* = 9.0 Hz); 7.66 (1H, d, *J* = 7.2 Hz); 7.72-7.74 (1H, m); 7.86 (1H, d, *J* = 7.8 Hz); 7.95 (1H, d, *J* = 7.8 Hz). ¹³C-NMR (150 MHz, CDCl₃), δ (ppm): 55.5; 102.1; 113.5 (2C); 120.2; 124.2; 127.9; 128.6 (2C); 128.8 (2C); 130.8 (2C); 131.0; 131.1; 133.1; 133.3; 134.3; 137.2; 142.0; 163.6; 167.5; 189.8. LC-MS (APCI⁺), *m/z*: 390.1 [M+H]⁺. Anal. calcd for C₂₃H₁₆ClNO₃: C, 70.86; H, 4.14; N, 3.59; found: C, 70.78; H, 4.22; N, 3.59.

Cyclocarbonylative Sonogashira of N-(4-chlorophenyl)-2-ethynylbenzamide (**6**) and 2-iodoanisole (**2c**) (Table 4, entry 4). Following the general procedure, 2.8 mg (0.004 mmol) of PdCl₂(PPh₃)₂, 255.7 mg (1.0 mmol) of *N*-(4-chlorophenyl)-2-ethynylbenzamide (**6**), 234.0 mg (1.0 mmol) of 2-iodoanisole (**2c**), 1.5 mL of Et₃N and 4 mL of CH₂Cl₂ were put in the autoclave charged with 20 atm of CO. The resulting mixture was stirred for 4 h at 100 °C. The crude product was purified through column chromatography (neutral Al₂O₃, *n*-hexane/AcOEt 3:1), obtaining 289 mg (yield 74%) of (*E*)-2-(4-chlorophenyl)-3-(2-(2-methoxyphenyl)-2-oxoethylidene)isoindolin-1-one ((*E*)-**7c**) and 12 mg (yield 3%) of (*Z*)-2-(4-chlorophenyl)-3-(2-(2-methoxyphenyl)-2-oxoethylidene)isoindolin-1-one ((*Z*)-**7c**).

(*E*)-**7c**. ¹H-NMR (600 MHz, CDCl₃), δ (ppm): 3.72 (3H, s); 6.63 (1H, s); 6.91 (1H, d, *J* = 8.4 Hz); 7.01-7.04 (1H, m); 7.33 (2H, d, *J* = 8.7 Hz); 7.44-7.47 (1H, m); 7.53 (2H, d, *J* = 8.7 Hz); 7.66-7.68 (1H, m); 7.73-7.77 (2H, m); 7.96 (1H, d, *J* = 7.8 Hz); 9.15 (1H, d, *J* = 8.4 Hz). ¹³C-NMR (150 MHz, CDCl₃), δ (ppm): 55.3; 110.5; 111.6; 120.8; 123.6; 127.5; 129.5; 129.6; 129.7 (2C); 130.3 (2C); 130.8; 131.7; 132.7; 133.6; 133.7; 133.9; 134.8; 147.6; 158.1; 167.0; 189.7. LC-MS (APCI⁺), *m/z*: 390.1 [M+H]⁺.

Anal. calcd for $C_{23}H_{16}ClNO_3$: C, 70.86; H, 4.14; N, 3.59; found: C, 70.77; H, 4.20; N, 3.59.

(*Z*)-**7c**. 1H -NMR (600 MHz, $CDCl_3$), δ (ppm): 3.89 (3H, s); 6.77 (1H, s); 6.92 (2H, t, $J = 7.8$ Hz); 7.13 (2H, d, $J = 8.7$ Hz); 7.25 (2H, d, $J = 8.7$ Hz); 7.38-7.40 (2H, m); 7.62-7.65 (1H, m); 7.69-7.72 (1H, m); 7.82 (1H, d, $J = 7.8$ Hz); 7.94 (1H, d, $J = 7.8$ Hz).

Cyclocarbonylative Sonogashira of N-(4-chlorophenyl)-2-ethynylbenzamide (6) and 1-chloro-4-iodobenzene (2d) with 20 atm of CO (Table 4, entry 5). Following the general procedure, 2.8 mg (0.004 mmol) of $PdCl_2(PPh_3)_2$, 255.7 mg (1.0 mmol) of *N*-(4-chlorophenyl)-2-ethynylbenzamide (**6**), 238.5 mg (1.0 mmol) of 1-chloro-4-iodobenzene (**2d**), 1.5 mL of Et_3N and 4 mL of CH_2Cl_2 were put in the autoclave charged with 20 atm of CO. The resulting mixture was stirred for 4 h at 100 °C. The crude product was purified through column chromatography (neutral Al_2O_3 , *n*-hexane/ $AcOEt$ 3:1), obtaining 201 mg (yield 51%) of (*E*)-2-(4-chlorophenyl)-3-(2-(4-chlorophenyl)-2-oxoethylidene)isoindolin-1-one ((*E*)-**7d**), 28 mg (yield 7%) of (*Z*)-2-(4-chlorophenyl)-3-(2-(4-chlorophenyl)-2-oxoethylidene)isoindolin-1-one ((*Z*)-**7d**) and 11 mg (yield 3%) of (*Z*)-3-(4-chlorobenzylidene)-2-(4-chlorophenyl)isoindolin-1-one (**8**).

(*E*)-**7d**. 1H -NMR (600 MHz, $CDCl_3$), δ (ppm): 6.45 (1H, s); 7.35 (2H, d, $J = 9.0$ Hz); 7.42 (2H, d, $J = 8.4$ Hz); 7.57 (2H, d, $J = 8.4$ Hz); 7.68 (1H, t, $J = 7.8$ Hz); 7.72-7.77 (3H, m); 7.96 (1H, d, $J = 7.2$ Hz); 8.94 (1H, d, $J = 7.8$ Hz). ^{13}C -NMR (150 MHz, $CDCl_3$), δ (ppm): 104.7; 123.8; 127.5; 128.9 (2C); 129.6 (2C); 130.1 (2C); 130.2 (2C); 132.1; 132.3; 133.7; 133.8; 134.5; 135.2; 137.2; 139.47; 149.9; 166.9; 188.3. LC-MS (APCI⁺), m/z : 394.1 $[M+H]^+$. Anal. calcd for $C_{22}H_{13}Cl_2NO_2$: C, 67.02; H, 3.32; N, 3.55; found: C, 67.08; H, 3.35; N, 3.55.

(*Z*)-**7d**. 1H -NMR (600 MHz, $CDCl_3$), δ (ppm): 6.56 (1H, s); 7.00 (2H, d, $J = 8.4$ Hz); 7.18 (2H, d, $J = 8.4$ Hz); 7.34 (2H, d, $J = 8.4$ Hz); 7.58 (2H, d, $J = 8.4$ Hz); 7.67 (1H, t, $J = 7.2$ Hz); 7.75 (1H, t, $J = 7.2$ Hz); 7.87 (1H, d, $J = 7.2$ Hz); 7.96 (1H, d, $J = 7.8$ Hz). ^{13}C -NMR (150 MHz, $CDCl_3$), δ (ppm): 100.8; 120.3; 124.4; 127.8; 128.4 (2C); 128.6; 128.7 (2C); 129.0 (2C); 129.7 (2C); 131.4; 133.3; 133.5; 134.4; 136.3; 137.1; 139.5; 143.5; 189.8. LC-MS (APCI⁺), m/z : 394.1 $[M+H]^+$. Anal. calcd for $C_{22}H_{13}Cl_2NO_2$: C, 67.02; H, 3.32; N, 3.55; found: C, 67.10; H, 3.37; N, 3.55.

8. ¹H-NMR (600 MHz, CDCl₃), δ (ppm): 6.75 (1H, s); 6.80 (2H, d, *J* = 8.4 Hz); 6.97 (2H, d, *J* = 8.4 Hz); 7.01 (2H, d, *J* = 8.7 Hz); 7.11 (2H, d, *J* = 8.7 Hz); 7.57 (1H, t, *J* = 7.2 Hz); 7.69 (1H, t, *J* = 7.2 Hz); 7.84 (1H, d, *J* = 7.8 Hz); 7.95 (1H, d, *J* = 7.8 Hz). ¹³C-NMR (150 MHz, CDCl₃), δ (ppm): 106.1; 110.6; 119.4; 124.0; 127.4; 127.5 (2C); 128.3 (2C); 128.4 (2C); 129.5; 129.8; 130.3 (2C); 130.7; 132.7; 134.2; 134.7; 138.3; 167.7. LC-MS (APCI⁺), *m/z*: 366.0 [M+H]⁺. Anal. calcd for C₂₁H₁₃Cl₂NO: C, 68.87; H, 3.58; N, 3.82; found: C, 68.81; H, 3.54; N, 3.81.

Cyclocarbonylative Sonogashira of N-(4-chlorophenyl)-2-ethynylbenzamide (6) and 1-chloro-4-iodobenzene (2d) with 40 atm of CO (Table 4, entry 6). Following the general procedure, 2.8 mg (0.004 mmol) of PdCl₂(PPh₃)₂, 255.7 mg (1.0 mmol) of *N*-(4-chlorophenyl)-2-ethynylbenzamide (**6**), 238.5 mg (1.0 mmol) of 1-chloro-4-iodobenzene (**2d**), 1.5 mL of Et₃N and 4 mL of CH₂Cl₂ were put in the autoclave charged with 40 atm of CO. The resulting mixture was stirred for 4 h at 100 °C. The composition of crude product was determined by ¹H-NMR analysis, resulting in a mixture of (*E*)-2-(4-chlorophenyl)-3-(2-(4-chlorophenyl)-2-oxoethylidene)isoindolin-1-one ((*E*)-**7d**), (*Z*)-2-(4-chlorophenyl)-3-(2-(4-chlorophenyl)-2-oxoethylidene)isoindolin-1-one ((*Z*)-**7d**) and (*Z*)-3-(4-chlorobenzylidene)-2-(4-chlorophenyl) isoindolin-1-one (**8**) in the molar ratio 86/10/4.

Cyclocarbonylative Sonogashira of N-(4-chlorophenyl)-2-ethynylbenzamide (6) and 1-iodonaphthalene (2f) (Table 4, entry 7). Following the general procedure, 2.8 mg (0.004 mmol) of PdCl₂(PPh₃)₂, 255.7 mg (1.0 mmol) of *N*-(4-chlorophenyl)-2-ethynylbenzamide (**6**), 254.1 mg (1.0 mmol) of 1-iodonaphthalene (**2f**), 1.5 mL of Et₃N and 4 mL of CH₂Cl₂ were put in the autoclave charged with 20 atm of CO. The resulting mixture was stirred for 4 h at 100 °C. The crude product was purified through column chromatography (neutral Al₂O₃, *n*-hexane/AcOEt 6:1), obtaining 283 mg (yield 69%) of (*E*)-2-(4-chlorophenyl)-3-(2-(naphthalen-1-yl)-2-oxoethylidene)isoindolin-1-one ((*E*)-**7f**) and 21 mg (yield 5%) of (*Z*)-2-(4-chlorophenyl)-3-(2-(naphthalen-1-yl)-2-oxoethylidene)isoindolin-1-one ((*Z*)-**7f**).

(*E*)-**7f**. ¹H-NMR (600 MHz, CDCl₃), δ (ppm): 6.41 (1H, s); 7.33 (2H, d, *J* = 8.7 Hz); 7.46 (1H, t, *J* = 7.8 Hz); 7.49 (2H, d, *J* = 8.7 Hz); 7.54 (1H, t, *J* = 7.2 Hz); 7.59 (1H, t, *J* = 7.2 Hz); 7.69-7.72 (2H, m);

7.76 (1H, t, $J = 7.8$ Hz); 7.89 (1H, d, $J = 8.4$ Hz); 7.96-8.00 (2H, m); 8.56 (1H, d, $J = 8.4$ Hz); 9.11 (1H, d, $J = 7.8$ Hz). ^{13}C -NMR (150 MHz, CDCl_3), δ (ppm): 109.0; 123.7; 124.4; 125.4; 126.5; 127.6; 127.7; 127.7; 128.5; 129.1; 129.5; 130.0 (4C); 130.1; 132.0; 132.2; 132.57; 133.8; 133.8; 135.0; 137.7; 149.1; 166.9; 192.9. LC-MS (APCI $^+$), m/z : 410.0 $[\text{M}+\text{H}]^+$. Anal. calcd for $\text{C}_{26}\text{H}_{16}\text{ClNO}_2$: C, 76.19; H, 3.93; N, 3.42; found: C, 76.07; H, 3.99; N, 3.43.

(*Z*)-**7f**. ^1H -NMR (600 MHz, CDCl_3), δ (ppm): 6.62 (1H, s); 6.84 (2H, d, $J = 8.4$ Hz); 6.88 (2H, d, $J = 8.4$ Hz); 7.40 (1H, t, $J = 7.8$ Hz); 7.49-7.54 (2H, m); 7.68 (1H, t, $J = 7.8$ Hz); 7.76 (1H, t, $J = 7.8$ Hz); 7.79-7.82 (2H, m); 7.89 (1H, d, $J = 7.2$ Hz); 7.95 (2H, t, $J = 6.6$ Hz); 8.32-8.33 (1H, m). ^{13}C -NMR (150 MHz, CDCl_3), δ (ppm): 104.3; 120.4; 124.0; 124.3; 125.6; 126.7; 127.5 (2C); 127.7; 127.9; 128.0; 129.1 (2C); 130.1; 130.1; 131.3; 133.0; 133.3; 133.5; 133.9; 135.5; 137.4; 142.8; 167.6; 193.5. LC-MS (APCI $^+$), m/z : 410.0 $[\text{M}+\text{H}]^+$. Anal. calcd for $\text{C}_{26}\text{H}_{16}\text{ClNO}_2$: C, 76.19; H, 3.93; N, 3.42; found: C, 76.11; H, 3.97; N, 3.43.

Cyclocarbonylative Sonogashira of N-(4-chlorophenyl)-2-ethynylbenzamide (6) and 4-iodotoluene (2g) (Table 4, entry 8). Following the general procedure, 2.8 mg (0.004 mmol) of $\text{PdCl}_2(\text{PPh}_3)_2$, 255.7 mg (1.0 mmol) of *N*-(4-chlorophenyl)-2-ethynylbenzamide (**6**), 92.1 mg (1.0 mmol) of 4-iodotoluene (**2g**), 1.5 mL of Et_3N and 4 mL of CH_2Cl_2 were put in the autoclave charged with 20 atm of CO. The resulting mixture was stirred for 4 h at 100 °C. The crude product was purified through column chromatography (neutral Al_2O_3 , *n*-hexane/AcOEt 3:1), obtaining 251 mg (yield 67%) of (*E*)-2-(4-chlorophenyl)-3-(2-oxo-2-(*p*-tolyl)ethylidene)isoindolin-1-one ((*E*)-**7g**) and 26 mg (yield 7%) of (*Z*)-2-(4-chlorophenyl)-3-(2-oxo-2-(*p*-tolyl)ethylidene)isoindolin-1-one ((*Z*)-**7g**).

(*E*)-**7g**. ^1H -NMR (600 MHz, CDCl_3), δ (ppm): 2.39 (3H, s); 6.51 (1H, s); 7.24 (2H, d, $J = 8.4$ Hz); 7.36 (2H, d, $J = 8.4$ Hz); 7.56 (2H, d, $J = 8.4$ Hz); 7.65 (1H, t, $J = 7.8$ Hz); 7.70 (1H, t, $J = 7.8$ Hz); 7.74 (2H, d, $J = 8.4$ Hz); 7.94 (1H, d, $J = 7.2$ Hz); 8.91 (1H, d, $J = 7.8$ Hz). ^{13}C -NMR (150 MHz, CDCl_3), δ (ppm): 21.6; 105.6; 123.6; 127.4; 128.4 (2C); 129.3 (2C); 129.5; 130.1 (2C); 130.1 (2C); 131.8; 132.5; 133.6; 133.9; 135.0; 136.4; 143.9; 148.8; 166.9; 189.4. LC-MS (APCI $^+$), m/z : 374.1 $[\text{M}+\text{H}]^+$. Anal. calcd for $\text{C}_{23}\text{H}_{16}\text{ClNO}_2$: C, 73.90; H, 4.31; N, 3.75; found: C, 74.01; H, 4.25; N, 3.76.

(Z)-**7g**. $^1\text{H-NMR}$ (600 MHz, CDCl_3), δ (ppm): 2.40 (3H, s); 6.61 (1H, s); 7.01 (2H, d, $J = 9.0$ Hz); 7.15 (2H, d, $J = 9.0$ Hz); 7.17 (2H, d, $J = 8.1$ Hz); 7.56 (2H, d, $J = 8.1$ Hz); 7.66 (1H, t, $J = 7.2$ Hz); 7.74 (1H, t, $J = 7.8$ Hz); 7.87 (1H, d, $J = 7.8$ Hz); 7.96 (1H, d, $J = 7.8$ Hz). $^{13}\text{C-NMR}$ (150 MHz, CDCl_3), δ (ppm): 21.7; 101.8; 120.2; 124.3; 127.9; 128.5 (2C); 128.6 (2C); 128.9 (2C); 129.0 (2C); 131.1; 133.1; 133.3; 134.4; 135.5; 137.3; 142.6; 144.0; 167.5; 190.7. LC-MS (APCI $^+$), m/z : 374.1 $[\text{M}+\text{H}]^+$. Anal. calcd for $\text{C}_{23}\text{H}_{16}\text{ClNO}_2$: C, 73.90; H, 4.31; N, 3.75; found: C, 73.99; H, 4.23; N, 3.76.

Cyclocarbonylative Sonogashira of N-(4-chlorophenyl)-2-ethynylbenzamide (6) and 2-iodotoluene (2h) (Table 4, entry 9). Following the general procedure, 2.8 mg (0.004 mmol) of $\text{PdCl}_2(\text{PPh}_3)_2$, 255.7 mg (1.0 mmol) of *N*-(4-chlorophenyl)-2-ethynylbenzamide (**6**), 92.1 mg (1.0 mmol) of 2-iodotoluene (**2h**), 1.5 mL of Et_3N and 4 mL of CH_2Cl_2 were put in the autoclave charged with 20 atm of CO. The resulting mixture was stirred for 4 h at 100 $^\circ\text{C}$. The crude product was purified through column chromatography (neutral Al_2O_3 , *n*-hexane/AcOEt 3:1), obtaining 225 mg (yield 60%) of (*E*)-2-(4-chlorophenyl)-3-(2-oxo-2-(*o*-tolyl)ethylidene)isoindolin-1-one ((*E*)-**7h**) and 19 mg (yield 5%) of (*Z*)-2-(4-chlorophenyl)-3-(2-oxo-2-(*o*-tolyl)ethylidene)isoindolin-1-one ((*Z*)-**7h**).

(*E*)-**7h**. $^1\text{H-NMR}$ (600 MHz, CDCl_3), δ (ppm): 2.51 (3H, s); 6.24 (1H, s); 7.20-7.26 (2H, m); 7.31 (2H, d, $J = 8.4$ Hz); 7.36 (1H, t, $J = 7.8$ Hz); 7.45 (1H, d, $J = 7.2$ Hz); 7.52 (2H, d, $J = 8.4$ Hz); 7.69 (1H, t, $J = 7.8$ Hz); 7.75 (1H, t, $J = 7.2$ Hz); 7.97 (1H, d, $J = 7.2$ Hz); 9.00 (1H, d, $J = 7.8$ Hz). $^{13}\text{C-NMR}$ (150 MHz, CDCl_3), δ (ppm): 20.7; 108.7; 123.7; 125.8; 127.5; 128.5; 129.6; 130.1 (2C); 130.1 (2C); 131.2; 131.7; 132.0; 132.3; 133.8; 133.9; 135.1; 137.5; 1140.0; 148.8; 166.9; 193.4. LC-MS (APCI $^+$), m/z : 374.1 $[\text{M}+\text{H}]^+$. Anal. calcd for $\text{C}_{23}\text{H}_{16}\text{ClNO}_2$: C, 73.90; H, 4.31; N, 3.75; found: C, 74.00; H, 4.24; N, 3.76.

(*Z*)-**7h**. $^1\text{H-NMR}$ (600 MHz, CDCl_3), δ (ppm): 2.24 (3H, s); 6.47 (1H, s); 6.96 (2H, d, $J = 9.0$ Hz); 7.15 (2H, d, $J = 9.0$ Hz); 7.18-7.20 (2H, m); 7.56-7.62 (2H, m); 7.66 (1H, t, $J = 7.2$ Hz); 7.74 (1H, t, $J = 7.8$ Hz); 7.85 (1H, d, $J = 7.8$ Hz); 7.95 (1H, d, $J = 7.8$ Hz).

Cyclocarbonylative Sonogashira of N-(4-chlorophenyl)-2-ethynylbenzamide (6) and 4-iodobenzonitrile (2e) (Scheme S4). Following the general procedure, 2.8 mg (0.004 mmol) of $\text{PdCl}_2(\text{PPh}_3)_2$, 255.7 mg (1.0

mmol) of *N*-(4-chlorophenyl)-2-ethynylbenzamide (**6**), 229.0 mg (1.0 mmol) of 4-iodobenzonitrile (**2e**), 1.5 mL of Et₃N and 4 mL of CH₂Cl₂ were put in the autoclave charged with 20 atm of CO. The resulting mixture was stirred for 4 h at 100 °C. The crude product was purified through column chromatography (neutral Al₂O₃, *n*-hexane/AcOEt 3:1), obtaining 70 mg (yield 18%) of (*E*)-4-(2-(2-(4-chlorophenyl)-3-oxoisindolin-1-ylidene)acetyl)benzonitrile ((*E*)-**7e**), 20 mg (yield 5%) of (*Z*)-4-(2-(2-(4-chlorophenyl)-3-oxoisindolin-1-ylidene)acetyl)benzonitrile ((*Z*)-**7e**) and 15 mg (yield 4%) of (*Z*)-4-((2-(4-chlorophenyl)-3-oxoisindolin-1-ylidene)methyl)benzonitrile (**9**).

(*E*)-**7e**. ¹H-NMR (600 MHz, CDCl₃), δ (ppm): 6.45 (1H, s); 7.35 (2H, d, *J* = 8.4 Hz); 7.59 (2H, d, *J* = 8.4 Hz); 7.72-7.80 (4H, m); 7.90 (2H, d, *J* = 8.4 Hz); 8.00 (1H, d, *J* = 7.8 Hz); 9.04 (1H, d, *J* = 7.8 Hz). ¹³C-NMR (150 MHz, CDCl₃), δ (ppm): 103.7; 116.0; 117.9; 123.9; 127.7; 128.5 (2C); 129.4; 130.0 (2C); 130.3 (2C); 132.1; 132.5 (2C); 132.6; 133.6; 134.0; 135.4; 142.3; 151.3; 166.9; 187.8. LC-MS (APCI⁺), *m/z*: 385.2 [M+H]⁺. Anal. calcd for C₂₃H₁₃ClN₂O₂: C, 71.79; H, 3.41; N, 7.28; found: C, 71.71; H, 3.46; N, 7.27.

(*Z*)-**7e**. ¹H-NMR (600 MHz, CDCl₃), δ (ppm): 6.57 (1H, s); 7.00 (2H, d, *J* = 8.4 Hz); 7.20 (2H, d, *J* = 8.4 Hz); 7.67 (2H, d, *J* = 8.4 Hz); 7.70-7.78 (4H, m); 7.88 (1H, d, *J* = 7.2 Hz); 7.97 (1H, d, *J* = 7.2 Hz).

9. ¹H-NMR (600 MHz, CDCl₃), δ (ppm): 6.75 (1H, s); 6.97 (2H, d, *J* = 8.4 Hz); 7.00 (2H, d, *J* = 8.7 Hz); 7.11 (2H, d, *J* = 8.7 Hz); 7.27 (2H, d, *J* = 8.4 Hz); 7.61 (1H, t, *J* = 7.8 Hz); 7.72 (1H, t, *J* = 7.2 Hz); 7.86 (1H, d, *J* = 7.8 Hz); 7.96 (1H, d, *J* = 7.8 Hz). ¹³C-NMR (150 MHz, CDCl₃), δ (ppm): 104.7; 110.1; 118.5; 119.6; 124.2; 127.5; 128.3 (2C); 128.6 (2C); 129.6 (2C); 130.1; 130.9 (2C); 132.3; 133.1; 134.1; 136.5; 138.0; 138.4; 167.6. LC-MS (APCI⁺), *m/z*: 357.0 [M+H]⁺. Anal. calcd for C₂₂H₁₃ClN₂O: C, 74.06; H, 3.67; N, 7.85; found: C, 73.97; H, 3.74; N, 7.86.

Cyclocarbonylative Sonogashira of N-(4-chlorophenyl)-2-ethynylbenzamide (**6**) and 4-bromonitrobenzene (**2i**) (Scheme 4). Following the general procedure, 2.8 mg (0.004 mmol) of PdCl₂(PPh₃)₂, 255.7 mg (1.0 mmol) of *N*-(4-chlorophenyl)-2-ethynylbenzamide (**6**), 202.0 mg (1.0 mmol) of 4-bromonitrobenzene (**2i**), 1.5 mL of Et₃N and 4 mL of CH₂Cl₂ were put in the autoclave

charged with 20 atm of CO. The resulting mixture was stirred for 4 h at 100 °C. The crude product was purified through column chromatography (SiO₂, *n*-hexane/AcOEt 9:1), obtaining 218 mg (yield 85%) of 2-(4-chlorophenyl)-3-methyleneisoindolin-1-one (**10**).⁴⁵

¹H-NMR (600 MHz, CDCl₃), δ (ppm): 4.83 (1H, d, *J* = 2.4 Hz); 5.28 (1H, d, *J* = 2.4 Hz); 7.36 (2H, d, *J* = 9.0 Hz); 7.51 (2H, d, *J* = 9.0 Hz); 7.58-7.61 (1H, m); 7.67-7.69 (1H, m); 7.79 (1H, d, *J* = 7.6 Hz); 7.94 (1H, d, *J* = 7.6 Hz). ¹³C-NMR (150 MHz, CDCl₃), δ (ppm): 90.4; 120.1; 123.6; 129.3 (2C); 129.6 (2C); 129.9; 132.5; 133.1; 133.8; 135.0; 136.2; 142.8; 166.5. LC-MS (APCI⁺), *m/z*: 256.0 [M+H]⁺. Anal. calcd for C₁₅H₁₀ClNO: C, 70.46; H, 3.94; N, 5.48; found: 70.54; H, 3.88; N, 5.47.

Cyclic Sonogashira reaction of N-(4-chlorophenyl)-2-ethynylbenzamide (6) and 1-chloro-4-iodobenzene (2d). In a 25 mL Carius tube sealed with a Teflon valve, *N*-(4-chlorophenyl)-2-ethynylbenzamide (**6**) (255.7 mg, 1.0 mmol), 1-chloro-4-iodobenzene (**2d**) (238.5 mg, 1.0 mmol), PdCl₂(PPh₃)₂ (2.8 mg, 0.004 mmol), Et₃N (1.5 mL) and CH₂Cl₂ (4 mL) were mixed together. The resulting mixture was left under stirring for 4 h at 100 °C, then it was hydrolyzed with H₂O (20 mL) and extracted with CH₂Cl₂ (3×30 mL). The combined organic phases were washed with brine (50 mL), dried over anhydrous Na₂SO₄ and the solvent was removed under vacuum. The crude product was purified by column chromatography (neutral Al₂O₃, *n*-hexane/AcOEt 6:1), to give 319 mg (yield 87%) of (Z)-3-(4-chlorobenzylidene)-2-(4-chlorophenyl)isoindolin-1-one (**8**).

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at

Supplementary schemes, ¹H-NMR and ¹³C-NMR spectra for all the pure compounds.

AUTHOR INFORMATION

Corresponding Author

Laura Antonella Aronica

Affiliation: *Dipartimento di Chimica e Chimica Industriale, Università di Pisa, Via Giuseppe Moruzzi 13,
56124 Pisa, Italy*

ORCID: orcid.org/0000-0002-1771-2667

Email: laura.antonella.aronica@unipi.it

Authors**Gianluigi Albano**

Affiliations: *Dipartimento di Chimica e Chimica Industriale, Università di Pisa, Via Giuseppe Moruzzi 13,
56124 Pisa, Italy*

*Present address: Dipartimento di Chimica, Università degli Studi di Bari “Aldo Moro”, Via
Edoardo Orabona 4, 70126 Bari, Italy*

ORCID: orcid.org/0000-0002-2466-5598

Stefano Giuntini

Affiliations: *Dipartimento di Chimica “Ugo Schiff”, Università degli Studi di Firenze, Via della Lastruccia 3,
50019 Sesto Fiorentino, Italy*

Centro di Risonanze Magnetiche (CERM), Università degli Studi di Firenze and Consorzio

*Interuniversitario Risonanze Magnetiche di Metallo Proteine (CIRMMP), Via Luigi Sacconi 6,
50019 Sesto Fiorentino, Italy*

ORCID: orcid.org/0000-0002-2292-8163

Complete contact information is available at

Notes

The authors declare no competing financial interest.

REFERENCES

- (1) Leyte-Lugo, M.; Britton, E. R.; Foil, D. H.; Brown, A. R.; Todd, D. A.; Rivera-Chávez, J.; Oberlies, N. H.; Cech, N. B. Secondary metabolites from the leaves of the medicinal plant goldenseal (*Hydrastis canadensis*). *Phytochem. Lett.* **2017**, *20*, 54.
- (2) Comins, D. L.; Schilling, S.; Zhang, Y. Asymmetric Synthesis of 3-Substituted Isoindolinones: Application to the Total Synthesis of (+)-Lennoxamine. *Org. Lett.* **2005**, *7*, 95.
- (3) Valencia, E.; Freyer, A. J.; Shamma, M.; Fajardo, V. (±)-Nuevamine, an isoindoloisoquinoline alkaloid, and (±)-lennoxamine, an isoindolobenzazepine. *Tetrahedron Lett.* **1984**, *25*, 599.
- (4) Narmani, A.; Teponno, R. B.; Helaly, S. E.; Arzanlou, M.; Stadler, M. Cytotoxic, anti-biofilm and antimicrobial polyketides from the plant associated fungus *Chaetosphaeronema achilleae*. *Fitoterapia* **2019**, *139*, 104390.
- (5) Zhao, J.; Liu, J.; Shen, Y.; Tan, Z.; Zhang, M.; Chen, R.; Zhao, J.; Zhang, D.; Yu, L.; Dai, J. Stachybotrysams A–E, prenylated isoindolinone derivatives with anti-HIV activity from the fungus *Stachybotrys chartarum*. *Phytochem. Lett.* **2017**, *20*, 289.
- (6) Wang, K.; Bao, L.; Qi, Q.; Zhao, F.; Ma, K.; Pei, Y.; Liu, H. Erinacerins C–L, Isoindolin-1-ones with α -Glucosidase Inhibitory Activity from Cultures of the Medicinal Mushroom *Herichium erinaceus*. *J. Nat. Prod.* **2015**, *78*, 146.
- (7) Chen, S.; Liu, Z.; Liu, Y.; Lu, Y.; He, L.; She, Z. New depsidones and isoindolinones from the mangrove endophytic fungus *Meyerozyma guilliermondii* (HZ-Y2) isolated from the South China Sea. *Beilstein J. Org. Chem.* **2015**, *11*, 1187.
- (8) Chen, L.; Li, Z.-H.; Yao, J.-N.; Peng, Y.-L.; Huang, R.; Feng, T.; Liu, J.-K. Isoindolinone-containing meroterpenoids with α -glucosidase inhibitory activity from mushroom *Herichium caput-medusae*. *Fitoterapia* **2017**, *122*, 107.
- (9) Fazal Hussainz, S.; Shamma, M. The catabolism of phthalideisoquinoline alkaloids. *Tetrahedron Lett.* **1980**, *21*, 1693.
- (10) Lamblin, M.; Couture, A.; Deniau, E.; Grandclaudeon, P. A concise first total synthesis of narceine imide. *Org. Biomol. Chem.* **2007**, *5*, 1466.
- (11) Chia, Y.-C.; Chang, F.-R.; Teng, C.-M.; Wu, Y.-C. Aristolactams and Dioxoaporphines from *Fissistigma balansae* and *Fissistigma oldhamii*. *J. Nat. Prod.* **2000**, *63*, 1160.

- (12) Valencia, E.; Fajardo, V.; Freyer, A. J.; Shamma, M. Magallanesine: an isoindolobenzazocine alkaloid. *Tetrahedron Lett.* **1985**, 26, 993.
- (13) Li, Y.; Wu, C.; Liu, D.; Proksch, P.; Guo, P.; Lin, W. Chartarlactams A–P, Phenylspirodrimanes from the Sponge-Associated Fungus *Stachybotrys chartarum* with Antihyperlipidemic Activities. *J. Nat. Prod.* **2014**, 77, 138.
- (14) Moreau, A.; Couture, A.; Deniau, E.; Grandclaudeon, P. A New Route to Aristocularine Alkaloids: Total Synthesis of Aristoyagonine. *J. Org. Chem.* **2004**, 69, 4527.
- (15) Kumar, V.; Poonam; Prasad, A. K.; Parmar, V. S. Naturally occurring aristolactams, aristolochic acids and dioxoaporphines and their biological activities. *Nat. Prod. Rep.* **2003**, 20, 565.
- (16) Hatoum, F.; Engler, J.; Zelmer, C.; Wißen, J.; Motti, C. A.; Lex, J.; Oelgemöller, M. Photodecarboxylative addition of carboxylates to phthalimides: a concise access to biologically active 3-(alkyl and aryl)methylene-1H-isoindolin-1-ones. *Tetrahedron Lett.* **2012**, 53, 5573.
- (17) Mata, R.; Morales, I.; Pérez, O.; Rivero-Cruz, I.; Acevedo, L.; Enriquez-Mendoza, I.; Bye, R.; Franzblau, S.; Timmermann, B. Antimycobacterial Compounds from *Piper sanctum*. *J. Nat. Prod.* **2004**, 67, 1961.
- (18) Tabopda, T. K.; Ngoupayo, J.; Liu, J.; Mitaine-Offer, A.-C.; Tanoli, S. A. K.; Khan, S. N.; Ali, M. S.; Ngadjui, B. T.; Tsamo, E.; Lacaille-Dubois, M.-A.; Luu, B. Bioactive aristolactams from *Piper umbellatum*. *Phytochemistry* **2008**, 69, 1726.
- (19) Chen, Y.-C.; Chen, J.-J.; Chang, Y.-L.; Teng, C.-M.; Lin, W.-Y.; Wu, C.-C.; Chen, I.-S. A New Aristolactam Alkaloid and Anti-Platelet Aggregation Constituents from *Piper taiwanense*. *Planta Med.* **2004**, 70, 174.
- (20) Lan, Y.-H.; Chia, Y.-C.; Chang, F.-R.; Hwang, T.-L.; Liaw, C.-C.; Wu, Y.-C. Potential Anti-Inflammatory Activities of Bractelactone and other Compounds Isolated from *Fissistigma bracteolatum*. *Helv. Chim. Acta* **2005**, 88, 905.
- (21) Zhang, Y.-N.; Zhong, X.-G.; Zheng, Z.-P.; Hu, X.-D.; Zuo, J.-P.; Hu, L.-H. Discovery and synthesis of new immunosuppressive alkaloids from the stem of *Fissistigma oldhamii* (Hemsl.) Merr. *Biorg. Med. Chem.* **2007**, 15, 988.

- (22) Ge, Y.-W.; Zhu, S.; Shang, M.-Y.; Zang, X.-Y.; Wang, X.; Bai, Y.-J.; Li, L.; Komatsu, K.; Cai, S.-Q. Aristololactams and aporphines from the stems of *Fissistigma oldhamii* (Annonaceae). *Phytochemistry* **2013**, *86*, 201.
- (23) Kim, S. R.; Sung, S. H.; Kang, S. Y.; Koo, K. A.; Kim, S. H.; Ma, C. J.; Lee, H.-S.; Park, M. J.; Kim, Y. C. Aristolactam BII of *Saururus chinensis* Attenuates Glutamate-Induced Neurotoxicity in Rat Cortical Cultures Probably by Inhibiting Nitric Oxide Production. *Planta Med.* **2004**, *70*, 391.
- (24) Kato, Y.; Takemoto, M.; Achiwa, K. Prostanoids and Related Compounds. VI. Synthesis of Isoindolinone Derivatives Possessing Inhibitory Activity for Thromboxane A₂ Analog (U-46619)-Induced Vasoconstriction. *Chem. Pharm. Bull.* **1993**, *41*, 2003.
- (25) Kato, Y.; Takemoto, M.; Achiwa, K. Prostanoids and Related Compounds. VII. Synthesis and Inhibitory Activity of 1-Isoindolinone Derivatives Possessing Inhibitory Activity against Thromboxane A₂ Analog (U-46619)-Induced Vasoconstriction. *Chem. Pharm. Bull.* **1999**, *47*, 529.
- (26) Couture, A.; Deniau, E.; Grandclaudeon, P.; Rybalko-Rosen, H.; Léonce, S.; Pfeiffer, B.; Renard, P. Synthesis and biological evaluation of aristolactams. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3557.
- (27) Liu, J.-J.; Dermatakis, A.; Lukacs, C.; Konzelmann, F.; Chen, Y.; Kammlott, U.; Depinto, W.; Yang, H.; Yin, X.; Chen, Y.; Schutt, A.; Simcox, M. E.; Luk, K.-C. 3,5,6-Trisubstituted naphthostyrils as CDK2 inhibitors. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2465.
- (28) Choi, Y. L.; Kim, J. K.; Choi, S.-U.; Min, Y.-K.; Bae, M.-A.; Kim, B. T.; Heo, J.-N. Synthesis of aristolactam analogues and evaluation of their antitumor activity. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3036.
- (29) Nayyatip, S.; Thaichana, P.; Buayairaksa, M.; Tuntiwechapikul, W.; Meepowpan, P.; Nuntasaeen, N.; Pompimon, W. Aristolactam-Type Alkaloids from *Orophea enterocarpa* and Their Cytotoxicities. *Int. J. Mol. Sci.* **2012**, *13*, 5010.
- (30) Chen, X.; Zhao, S.; Li, H.; Wang, X.; Geng, A.; Cui, H.; Lu, T.; Chen, Y.; Zhu, Y. Design, synthesis and biological evaluation of novel isoindolinone derivatives as potent histone deacetylase inhibitors. *Eur. J. Med. Chem.* **2019**, *168*, 110.
- (31) Youn, S. W. Transition-Metal-Catalyzed Annulative Coupling Cascade for the Synthesis of 3-Methyleneisoindolin-1-ones. *Synthesis* **2020**, *52*, 807.

- (32) Kondo, Y.; Shiga, F.; Murata, N.; Sakamoto, T.; Yamanaka, H. Condensed heteroaromatic ring systems. XXIV. Palladium-catalyzed cyclization of 2-substituted phenylacetylenes in the presence of carbon monoxide. *Tetrahedron* **1994**, *50*, 11803.
- (33) Cho, C. S.; Shim, H. S.; Choi, H.-J.; Kim, T.-J.; Shim, S. C. Palladium-catalysed convenient synthesis of 3-methyleneisindolin-1-ones. *Synth. Commun.* **2002**, *32*, 1821.
- (34) Cao, H.; McNamee, L.; Alper, H. Syntheses of Substituted 3-Methyleneisindolin-1-ones By a Palladium-Catalyzed Sonogashira Coupling–Carbonylation–Hydroamination Sequence in Phosphonium Salt-Based Ionic liquids. *Org. Lett.* **2008**, *10*, 5281.
- (35) Marosvölgyi-Haskó, D.; Takács, A.; Riedl, Z.; Kollár, L. High-yielding synthesis of 1-isindolinone derivatives via palladium-catalysed cycloaminocarbonylation. *Tetrahedron* **2011**, *67*, 1036.
- (36) Xuan, Z.; Jung, D. J.; Jeon, H. J.; Lee, S.-g. Pd-Catalyzed Aminocarbonylation of the Blaise Reaction Intermediate: One-Pot Synthesis of (Z)-3-Methyleneisindolin-1-ones from Nitriles. *J. Org. Chem.* **2016**, *81*, 10094.
- (37) Ling, F.; Ai, C.; Lv, Y.; Zhong, W. Traceless Directing Group Assisted Cobalt-Catalyzed C–H Carbonylation of Benzylamines. *Adv. Synth. Catal.* **2017**, *359*, 3707.
- (38) Fukuyama, T.; Bando, T.; Ryu, I. Electron-Transfer-Induced Intramolecular Heck Carbonylation Reactions Leading to Benzolactones and Benzolactams. *Synthesis* **2018**, *50*, 3015.
- (39) Zhang, C.; Ding, Y.; Gao, Y.; Li, S.; Li, G. Palladium-Catalyzed Direct C–H Carbonylation of Free Primary Benzylamines: A Synthesis of Benzolactams. *Org. Lett.* **2018**, *20*, 2595.
- (40) Dong, W.; Xu, G.; Tang, W. Enantioselective palladium-catalyzed C(sp²)-H carbamoylation. *Tetrahedron* **2019**, *75*, 3239.
- (41) Fu, L.-Y.; Ying, J.; Qi, X.; Peng, J.-B.; Wu, X.-F. Palladium-Catalyzed Carbonylative Synthesis of Isoindolinones from Benzylamines with TFBen as the CO Source. *J. Org. Chem.* **2019**, *84*, 1421.
- (42) Gabriele, B.; Mancuso, R.; Zicarelli, I.; Salerno, G. A new approach to isoindolinone derivatives by sequential palladium iodide-catalyzed oxidative aminocarbonylation–heterocyclization of 2-ethynylbenzamides. *Tetrahedron Lett.* **2012**, *53*, 6694.

- (43) Mancuso, R.; Zicarelli, I.; Armentano, D.; Marino, N.; Giofrè, S. V.; Gabriele, B. Divergent Palladium Iodide Catalyzed Multicomponent Carbonylative Approaches to Functionalized Isoindolinone and Isobenzofuranimine Derivatives. *J. Org. Chem.* **2014**, *79*, 3506.
- (44) Gao, B.; Liu, S.; Lan, Y.; Huang, H. Rhodium-Catalyzed Cyclocarbonylation of Ketimines via C–H Bond Activation. *Organometallics* **2016**, *35*, 1480.
- (45) Ju, J.; Qi, C.; Zheng, L.; Hua, R. Synthesis of 3-methyleneisoindolin-1-ones via palladium-catalyzed C–Cl bond cleavage and cyclocarbonylation of ortho-chloro ketimines. *Tetrahedron Lett.* **2013**, *54*, 5159.
- (46) Wang, Z.; Zhu, F.; Li, Y.; Wu, X.-F. Palladium-Catalyzed Carbonylative Synthesis of 3-Methyleneisoindolin-1-ones from Ketimines with Hexacarbonylmolybdenum(0) as the Carbon Monoxide Source. *ChemCatChem* **2017**, *9*, 94.
- (47) Xu, Y.; Hu, W.; Tang, X.; Zhao, J.; Wu, W.; Jiang, H. Palladium-catalyzed Csp²–H carbonylation of aromatic oximes: selective access to benzo[d][1,2]oxazin-1-ones and 3-methyleneisoindolin-1-ones. *Chem. Commun.* **2015**, *51*, 6843.
- (48) Aronica, L. A.; Giannotti, L.; Tuci, G.; Zinna, F. Cyclocarbonylative Sonogashira Reactions of 1-Ethynylbenzyl Alcohols: Synthesis of 1-Carbonylmethylene-1,3-Dihydroisobenzofurans. *Eur. J. Org. Chem.* **2015**, *2015*, 4944.
- (49) Aronica, L. A.; Albano, G.; Giannotti, L.; Meucci, E. Synthesis of N-Heteroaromatic Compounds through Cyclocarbonylative Sonogashira Reactions. *Eur. J. Org. Chem.* **2017**, *2017*, 955.
- (50) Albano, G.; Morelli, M.; Aronica, L. A. Synthesis of Functionalised 3-Isochromanones by Silylcarbocyclisation/Desilylation Reactions. *Eur. J. Org. Chem.* **2017**, *2017*, 3473.
- (51) Albano, G.; Aronica, L. A. Potentiality and Synthesis of O- and N-Heterocycles: Pd-Catalyzed Cyclocarbonylative Sonogashira Coupling as a Valuable Route to Phthalans, Isochromans, and Isoindolines. *Eur. J. Org. Chem.* **2017**, *2017*, 7204.
- (52) Albano, G.; Aronica, L. A. Cyclization Reactions for the Synthesis of Phthalans and Isoindolines-. *Synthesis* **2018**, *50*, 1209.
- (53) Albano, G.; Morelli, M.; Lissia, M.; Aronica, L. A. Synthesis of Functionalised Indoline and Isoquinoline Derivatives through a Silylcarbocyclisation/Desilylation Sequence. *ChemistrySelect* **2019**, *4*, 2505.

- (54) Wu, X.-F.; Neumann, H.; Beller, M. Convenient and General Palladium-Catalyzed Carbonylative Sonogashira Coupling of Aryl Amines. *Angew. Chem. Int. Ed.* **2011**, *50*, 11142.
- (55) Qi, X.; Jiang, L.-B.; Li, C.-L.; Li, R.; Wu, X.-F. Palladium-Catalyzed One-Pot Carbonylative Sonogashira Reaction Employing Formic acid as the CO Source. *Chemistry – An Asian Journal* **2015**, *10*, 1870.
- (56) Wu, F.-P.; Peng, J.-B.; Qi, X.; Wu, X.-F. Palladium-catalyzed carbonylative Sonogashira coupling of aryl diazonium salts with formic acid as the CO source: the effect of 1,3-butadiene. *Catal. Sci. Technol.* **2017**, *7*, 4924.
- (57) Li, Y.; Hu, Y.; Wu, X.-F. Non-noble metal-catalysed carbonylative transformations. *Chem. Soc. Rev.* **2018**, *47*, 172.
- (58) Peng, J.-B.; Wu, X.-F. Ligand- and Solvent-Controlled Regio- and Chemodivergent Carbonylative Reactions. *Angew. Chem. Int. Ed.* **2018**, *57*, 1152.
- (59) Kel'in, A. V. Recent Advances in the Synthesis of 1,3-Diketones. *Curr. Org. Chem.* **2003**, *7*, 1691.
- (60) Kel'in, A. V.; Maioli, A. Recent Advances in the Chemistry of 1,3-Diketones: Structural Modifications and Synthetic Applications. *Curr. Org. Chem.* **2003**, *7*, 1855.
- (61) Simon, C.; Constantieux, T.; Rodriguez, J. Utilisation of 1,3-Dicarbonyl Derivatives in Multicomponent Reactions. *Eur. J. Org. Chem.* **2004**, *2004*, 4957.
- (62) Sloop, J. C.; Bumgardner, C. L.; Washington, G.; Loehle, W. D.; Sankar, S. S.; Lewis, A. B. Keto–enol and enol–enol tautomerism in trifluoromethyl- β -diketones. *J. Fluorine Chem.* **2006**, *127*, 780.
- (63) Aromí, G.; Gamez, P.; Reedijk, J. Poly beta-diketones: Prime ligands to generate supramolecular metallocusters. *Coord. Chem. Rev.* **2008**, *252*, 964.
- (64) Kavala, V.; Wang, C.-C.; Barange, D. K.; Kuo, C.-W.; Lei, P.-M.; Yao, C.-F. Synthesis of Isocoumarin Derivatives via the Copper-Catalyzed Tandem Sequential Cyclization of 2- Halo-N-phenyl Benzamides and Acyclic 1,3-Diketones. *J. Org. Chem.* **2012**, *77*, 5022.
- (65) Zolotareva, N. V.; Semenov, V. V. β -Diketones and their derivatives in sol–gel processes. *Russ. Chem. Rev.* **2013**, *82*, 964.
- (66) Kljun, J.; Turel, I. β -Diketones as Scaffolds for Anticancer Drug Design – From Organic Building Blocks to Natural Products and Metallodrug Components. *Eur. J. Inorg. Chem.* **2017**, *2017*, 1655.

- (67) Long, Y.; She, Z.; Liu, X.; Chen, Y. Synthesis of 1-Aminoisoquinolines by Gold(III)-Mediated Domino Reactions from 2-Alkynylbenzamides and Ammonium Acetate. *J. Org. Chem.* **2013**, 78, 2579.
- (68) Jithunsa, M.; Ueda, M.; Miyata, O. Copper(II)Chloride-Mediated Cyclization Reaction of N-Alkoxy-ortho-alkynylbenzamides. *Org. Lett.* **2011**, 13, 518.
- (69) Yao, B.; Jaccoud, C.; Wang, Q.; Zhu, J. Synergistic Effect of Palladium and Copper Catalysts: Catalytic Cyclizative Dimerization of ortho-(1-Alkynyl)benzamides Leading to Axially Chiral 1,3-Butadienes. *Chem. Eur. J.* **2012**, 18, 5864.
- (70) Kundu, N. G.; Khan, M. W. Palladium-Catalysed Heteroannulation with Terminal Alkynes: a Highly Regio- and Stereoselective Synthesis of (Z)-3-Aryl(alkyl)idene Isoindolin-1-ones. *Tetrahedron* **2000**, 56, 4777.