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Divergent Palladium Iodide Catalyzed Multicomponent Carbonylative Approaches to Functionalized Isoindolinone and Isobenzofuranimine Derivatives

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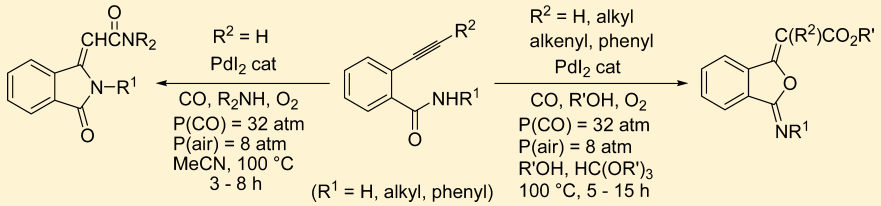
Supporting Information



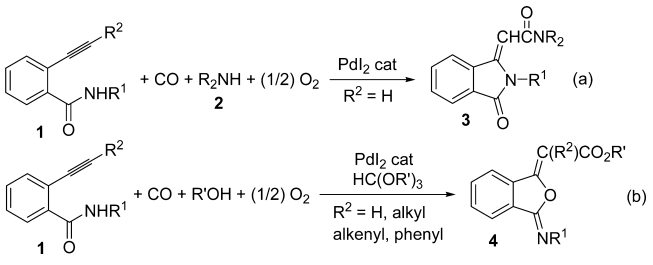
ABSTRACT: 2-Alkynylbenzamides underwent different reaction pathways when allowed to react under PdI_2-catalyzed oxidative carbonylation conditions, depending on the nature of the external nucleophile and reaction conditions. Thus, oxidative carbonylation of 2-ethynylbenzamides, bearing a terminal triple bond, carried out in the presence of a secondary amine as external nucleophile, selectively led to the formation of 3-[(dialkylcarbamoyl)methylene]isoindolin-1-ones through the intermediate formation of the corresponding 2-ynamide derivatives followed by intramolecular nucleophilic attack by the nitrogen of the benzamide moiety on the conjugated triple bond. On the other hand, 3-[(alkoxycarbonyl)methylene]-isobenzofuran-1(3*H*)imines were selectively obtained when the oxidative carbonylation of 2-alkynylbenzamides, bearing a terminal or an internal triple bond, was carried out in the presence of an alcohol R′OH (such as methanol or ethanol) as the external nucleophile and $HC(OR')_3$ as a dehydrating agent, necessary to avoid substrate hydrolysis. In this latter case, the reaction pathway leading to the isobenzofuranimine corresponded to the 5-*exo*-*dig* intramolecular nucleophilic attack of the oxygen of the benzamide moiety on the triple bond coordinated to the metal center followed by alkoxycarbonylation. The structures of representative products have been confirmed by X-ray crystallographic analysis.

INTRODUCTION

Isoindolinones are very important heterocyclic derivatives with many important applications.[1,2] In fact, many molecules containing the isoindolinone nucleus have shown important biological activities, including antimicriobial, antiproliferative and inhibitor of the MDM2-p53 protein−protein interaction effect.[1] We have recently communicated a novel carbonylation method for the synthesis of functionalized 3-methyleneisoindolin-1-ones[3,4] starting from readily available 2-ethynylbenzamides **1** (R^2 = H).[5] In this paper, a full account of this reactivity is reported that allows the direct synthesis of [3-[(dialkylcarbamoyl)methylene]isoindolin-1-ones **3** by PdI_2-catalyzed oxidative aminocarbonylation−*N*-heterocyclization of 2-ethynylbenzamides **1** (R^2 = H) with secondary amines **2**, according to Scheme 1a.

Very interestingly, it has also been found that 2-alkynylbenzamides **1**, bearing a terminal or an internal triple bond (R^2 = H, alkyl, alkenyl, phenyl), selectively lead to 3-

Scheme 1. Divergent Syntheses of Carbonylated Isoindolinone and Isobenzofuranimine Derivatives (3 and 4, Respectively) Starting from 2-Alkynylbenzamides 1 under Different Conditions



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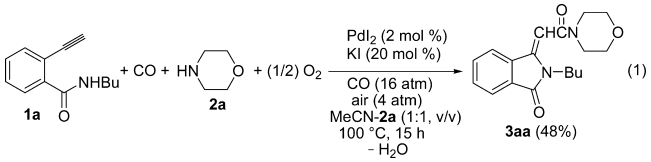
[(alkoxycarbonyl)methylene]isobenzofuran-1(3*H*)imines **4**, corresponding to *O*-heterocyclization, when the oxidative carbonylation reaction was carried out in the presence of an alcohol R′OH (such as methanol or ethanol) as the external nucleophile and $HC(OR')_3$ as a dehydrating agent (Scheme 1b). The possibility to obtain carbonylated isobenzofuranimines in one step by a multicomponent carbonylative approach is also very attractive, in view of the importance of this class of heterocycles.[6−8] Isobenzofuranimines have, in fact, been obtained in one step from very simple building blocks.[9]

RESULTS AND DISCUSSION

Synthesis of Carbonylated Isoindolinone Derivatives 3 by PdI_2-Catalyzed Aminocarbonylation−*N*-Heterocyclization of 2-Ethynylbenzamides 1 with Secondary Amines 2. The first substrate tested under PdI_2-catalyzed oxidative carbonylation conditions was *N*-butyl-2-ethynylbenzamide **1a** (R^1 = Bu, R^2 = H), readily available by ethynylation of *N*-butyl-2-iodobenzamide (see the Experimental Section for details). This substrate was initially allowed to react with CO, O_2, and morpholine (**2a**) at 100 °C for 15 h in a 1:1 (v/v) mixture of MeCN−morpholine as the solvent under a 4:1 mixture of CO−air (20 atm),[10] in the presence of catalytic amounts of PdI_2 (2 mol %) in conjunction with KI (KI/PdI_2 molar ratio = 10). Under these conditions, **1a** was converted into a ca. 2:1 *Z*/*E* mixture of 2-butyl-3-(2-morpholino-2-oxoethylidene)isoindolin-1-one **3aa**, which was isolated in 48% yield (eq 1 and entry 1, Table S1, Supporting Information). A



brief optimization study was then carried out in which the gas total pressure, substrate concentration, temperature, the amount of KI and morpholine, and the nature of the solvent were changed. The results, shown in Table S1 (Supporting Information), allowed the identification of the optimal conditions for this process, which corresponded to 100 °C under 40 atm of a 4:1 mixture of CO−air, in a 2:1 mixture of MeCN−morpholine as the solvent (substrate concentration = 0.05 mmol per mL of solvent). Under these conditions, isoindolinone **3aa** was obtained in 81% yield after 5 h (*Z*/*E* = 2.0, Table 1, entry 1).

The reactivity of other substrates **1b−e**, bearing different substituents on nitrogen, was then tested, with morpholine as the base and nucleophile (Table 1, entries 2−5). As can be seen from these data, the reaction also worked nicely with a benzyl (R^1 = Bn, Table 1, entry 2) and a phenyl (R^1 = Ph, Table 1, entry 3) substituent on nitrogen, with results similar to those obtained with R^1 = Bu (Table 1, entry 1). In both cases, the *Z* isomer was obtained as the major stereoisomer or sole diastereoisomer; the diastereoselectivity was higher with R^1 = Ph (**3ca**-*Z*, only *Z*, Table 1, entry 3) with respect to R^1 = Bn (**3ba**, *Z*/*E* = 2.2, Table 1, entry 2). Quite predictably, the reaction was slower when the nitrogen was substituted with a bulky group, such as in substrate **1d** (R^1 = *t*-Bu, Table 1, entry 4); in any case, an excellent yield of the corresponding carbonylated isoindolinone **3da**-*E* was still obtained (93%). Moreover, in this case, complete diastereoselectivity toward the *E* isomer was observed, probably due to the necessity to minimize the steric repulsion between the bulky substituent and the morpholine ring.

The structure of **3da**-*E* was confirmed by X-ray diffraction analysis, as shown in Figure S1 (Supporting Information). In the ^{1}H NMR spectrum of **3da**-*E*, the olefinic proton absorbed at 6.1 ppm, so a chemical shift around 6 ppm could be considered diagnostic for an *E* configuration around the exocyclic double bond of diastereoisomers **3aa**-*E* and **3ba**-*E*, while the olefinic proton for diastereoisomers **3aa**-*Z*, **3ba**-*Z*, and **3ca**-*Z* absorbed in the range 5.6−5.8 ppm (see the Experimental Section).

On the other hand, complete diastereoselectivity toward the isomer *Z* was observed when R^1 = H (**3ea**-*Z*, Table 1, entry 5), due to the stabilization by intramolecular hydrogen bonding between the NH group and the carbonyl of the exocyclic amido group, as confirmed by the X-ray crystallographic analysis for **3ea**-*Z* (Figure S2, Supporting Information).

The nature of the secondary amine was also changed, with substrates **1a** (R^1 = Bu) and **1d** (R^1 = *tert*-butyl). As can be seen from the results reported in Table 1, entries 6−10, high to excellent yields of the corresponding isoindolinones (76−96%) were also observed working with other secondary nucleophilic cyclic or acyclic amines such as piperidine **2b** (Table 1, entries 6 and 7), pyrrolidine **2c** (Table 1, entries 8 and 9), or dibutylamine **2d** (Table 1, entry 10). With substrate **1d** (R^1 = *tert*-butyl), again complete *E* diastereoselectivity was observed in the final products **3db**-*E* and **3dc**-*E* (Table 1, entries 7 and 9).

On the basis of what is already known on the PdI_2-catalyzed oxidative aminocarbonylation of terminal alkynes,[9,11] the reaction course leading to the isoindolinone derivatives **3** can be interpreted as occurring as shown in Scheme 2 (anionic iodide ligands are omitted for clarity). Thus, formation of an alkynylpalladium intermediate **I** takes place by the reaction between substrate **1a−e**, PdI_2, and the base, followed by CO insertion to give an alkynoylpalladium species **II**. Nucleophilic displacement by the amine then leads to the 2-ynamide intermediate **III** and Pd(0). The latter is reoxidized by the action of I_2 (formed in its turn by oxidation of HI, ensuing from the carbonylation process, and O_2),[12] while intermediate **III** undergoes 5-*exo*-*dig* *N*-cyclization by intramolecular conjugate addition to give the final product **3**. Clearly, the formation of alkynylpalladium complex **I** (and therefore of **II** and **III**) is possible because the starting substrate **1a−e** bears a terminal triple bond. Accordingly, no reaction occurred with 2-alkynylbenzamides bearing an internal triple bond.

Synthesis of Carbonylated Isobenzofuranimine Derivatives 4 by PdI_2-Catalyzed *O*-Heterocyclization−Alkoxycarbonylation of 2-Alkynylbenzamides 1. As already noted, 2-alkynylbenzamides, bearing an internal triple bond, cannot undergo aminocarbonylation. These substrates, however, did react under alkoxycarbonylation conditions since, in this case, the reaction mechanism may start with the coordination of the triple bond to PdI_2 followed by intramolecular nucleophilic attack (either *exo* or *endo*) and alkoxycarbonylation (Scheme 3).[9,11,13]

Very interestingly, under alkoxycarbonylation conditions (in MeOH as the solvent, with a substrate concentration of 0.02 mmol/mL of MeOH, in the presence of 2 mol % PdI_2 and 20 mol % of KI, under 40 atm of a 4:1 mixture of CO−air at 100 °C for 5 h), 2-(hex-1-ynyl)-*N*-phenylbenzamide **1f** underwent *O*-cyclization rather than *N*-cyclization, followed by alkoxycarbonylation, to give a mixture of methyl 2-[3-

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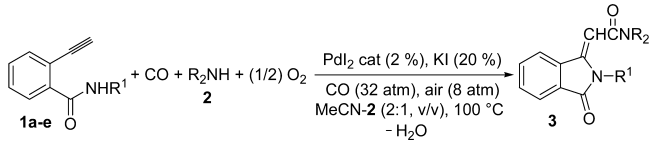
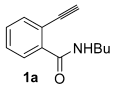
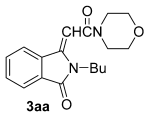
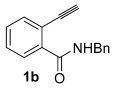
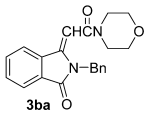
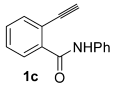
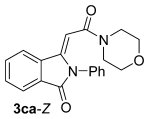
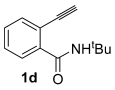
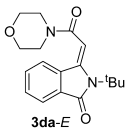
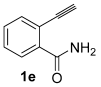
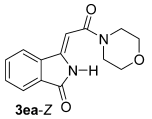
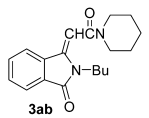
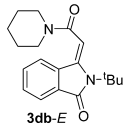
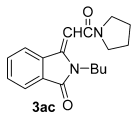
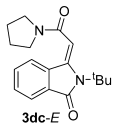
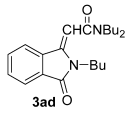
Table 1. Synthesis of [3-[(Dialkylcarbamoyl)methylene]isoindolin-1-ones 3 by PdI_2-Catalyzed Aminocarbonylation−*N*-Heterocyclization of 2-Ethynylbenzamides 1a−e[a]



entry	1	R^1	R_2NH	time (h)	3	yield of 3[b] (%)
1		Bu	 2a	5	 3aa	81[c]
2		Bn	**2a**	5	 3ba	83[d]
3		Ph	**2a**	3	 3ca-*Z*	86[e]
4		*t*-Bu	**2a**	8	 3da-*E*	93[f]
5		H	**2a**	5	 3ea-*Z*	65[g]
6	**1a**	Bu	 2b	5	 3ab	90[h]
7	**1d**	*t*-Bu	**2b**	5	 3db-*E*	76[i]
8	**1a**	Bu	 2c	5	 3ac	86[j]
9	**1d**	*t*-Bu	**2c**	5	 3dc-*E*	82[i]
10	**1a**	Bu	Bu_2NH 2d	5	 3ad	96[k]

[a]All reactions were carried out in a MeCN−R_2NH mixture (2:1, v/v) as the solvent (concentration of **1** = 0.05 mmol per mL of solvent) at 100 °C and under 40 atm (at 25 °C) of a 4:1 mixture of CO−air, in the presence of 2 mol % of PdI_2 in conjunction with an excess of KI (KI/PdI_2 molar ratio = 10). Conversion of **1** was quantitative in all cases. [b]Isolated yield based on starting **1**. [c]*Z*/*E* ratio = 2.0 (determined by ^{1}H NMR). [d]*Z*/*E* ratio = 2.2 (determined by ^{1}H NMR). [e]The reaction was selective toward the formation of the *Z* isomer. [f]The reaction was selective toward the formation of the *E* isomer. The structure of **3da**-*E* was confirmed by X-ray diffraction analysis. [g]The reaction was selective toward the formation of the *Z* isomer. The structure of **3ea**-*Z* was confirmed by X-ray diffraction analysis. [h]*Z*/*E* ratio = 1.0 (determined by ^{1}H NMR). [i]The reaction was selective toward the formation of the *E* isomer. [j]*Z*/*E* ratio = 1.8 (determined by ^{1}H NMR). [k]*Z*/*E* ratio = 1.0 (determined by isolation of the diastereoisomers after column chromatography).

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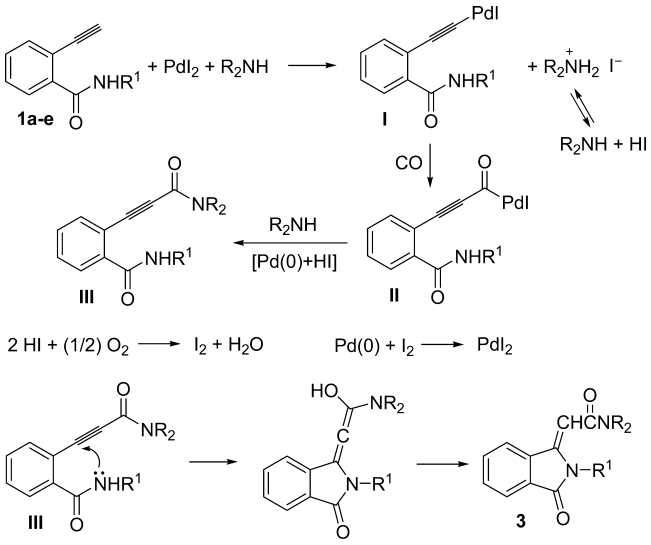
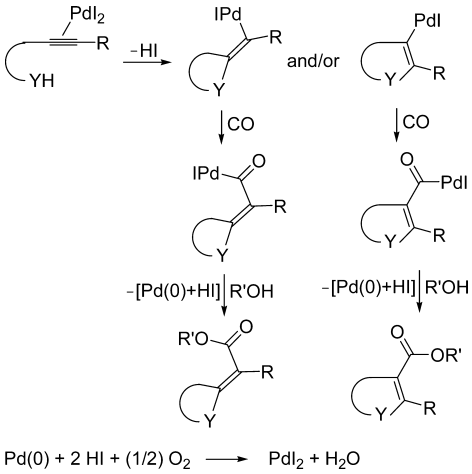
Scheme 2. Plausible Reaction Mechanism for the PdI_2/KI-Catalyzed Carbonylative *N*-Cyclization of 2-Ethynylbenzamides 1a−e Leading to Carbonylated Isoindolinones 3[a]

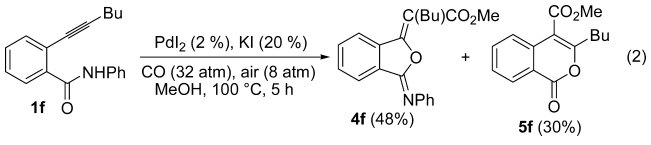


[a]Anionic iodide ligands are omitted for clarity.

Scheme 3. General Mechanism for the PdI_2-Catalyzed Heterocyclization−Alkoxycarbonylation of Acetylenic Substrates Bearing a Suitably Placed Nucleophilic Group (Y = O or NR″)



(phenylimino)isobenzofuran-1(3*H*)-ylidene]hexanoate **4f** (*Z*/*E* ca. 1.4) and methyl 3-butyl-1-oxo-1*H*-isochromene-4-carboxylate **5f** (eq 2).



Formation of **4f** clearly corresponded to the 5-*exo*-*dig* nucleophilic attack of the amido oxygen to the coordinated triple bond to give the vinylpalladium complex **IV** followed by alkoxycarbonylation (Scheme 4, path a. Partial isomerization of intermediate **IV**[14] accounted for the formation of the *E*/*Z* mixture). On the other hand, the involvement of water with elimination of aniline is necessary to justify the formation of **5f**. It is conceivable that 6-*endo*-*dig* nucleophilic attack of the amido oxygen to the coordinated triple bond gives the vinylpalladium complex **V**. Hydrolysis of the exocyclic imino group of **V** would then lead to the corresponding lactone-vinylpalladium intermediate **VI**, whose alkoxycarbonylation would eventually afford **5f** (Scheme 4, path b). However, the possibility of an HI-promoted nucleophilic attack by water to the amidic carbonyl of **1f**, with formation of tetrahedral intermediate **VII**, cannot be ruled out. The latter would then undergo 6-*endo*-*dig* *O*-cyclization to give complex **VIII**, followed by elimination of aniline from the HO(C)NHPh moiety to afford the same lactone-vinylpalladium intermediate **VI** seen before (Scheme 4, path c).

In order to minimize the formation of byproduct **5f**, the next experiments were carried out in the presence of a dehydrating agent, such as trimethyl orthoformate.[15] Indeed, when $HC(OMe)_3$ was used as a cosolvent together with MeOH (2:1 v/v, R = Me), **4f** was selectively obtained in 80% yield, without any formation of **5f** (Table 2, entry 1). The reaction with a higher alcohol, such as ethanol (R = Et), also afforded a high yield of the corresponding isobenzofuranimine derivative **4f′** (83%, Table 2, entry 2). The protocol was then extended to other 2-alkynylbenzamides bearing different substituents on nitrogen and on the triple bond. As shown in Table 2, the nitrogen could be successfully substituted with an alkyl or a benzyl group, while the triple bond could also bear a phenyl or a 1-cyclohexenyl group. The reaction also worked nicely with a terminal triple bond, as shown by entries 8−12. In this latter case, the process was consistently selective toward the formation of the *E* stereoisomer. The structure of representative products, in particular (*E*)-methyl 2-[3-(*tert*-butylimino)-isobenzofuran-1(3*H*)-ylidene]acetate **4d**-*E* and (*E*)-methyl 2-[3-(phenylimino)isobenzofuran-1(3*H*)-ylidene]-2-phenylacetate **4i**-*E*, was confirmed by X-ray diffractometric analysis, as shown in Figures S3 and S4, respectively (Supporting Information). A chemical shift for the olefinic proton around 6.0 ppm was diagnostic of *E* stereochemistry for products **4a**-*E*, **4a′**-*E*, **4b**-*E*, **4c**-*E*, and **4d**-*E*. On the other hand, for products **4f−k**, the chemical shift of aromatic proton at ca. 8.2−8.4 ppm was diagnostic for the *E* diastereoisomer, while the aromatic absorptions at ca. 8.5 ppm and 7.9−8.0 ppm were characteristic of the *Z* distereoisomer (see the Experimental Section).

CONCLUSIONS

In conclusion, we have developed divergent, multicomponent carbonylative approaches to functionalized isoindolinone and isobenzofuranimine derivatives (**3** and **4**, respectively) starting from readily available 2-alkynylbenzamides **1**. In particular, by reacting 2-ethynylbenzamides (bearing a terminal triple bond) with CO, a nucleophilic secondary amine (**2**), and O_2 in the presence of the PdI_2/KI catalytic system, [3-[(dialkylcarbamoyl)methylene]isoindolin-1-ones **3** were selectively obtained by oxidative monoaminocarbonylation of the triple bond followed by *N*-cyclization, occurring through intramolecular conjugate addition to the 2-ynamide intermediate. On the other hand, 3-[(alkoxycarbonyl)methylene]-isobenzofuran-1(3*H*)imines **4** were selectively formed from 2-alkynylbenzamides **1** bearing a terminal as well as an internal triple bond, through 5-*exo*-*dig* *O*-cyclyzation−alkoxycarbonylation, taking place in a ROH/$HC(OR)_3$ mixture (R = Me, Et) as the solvent in the presence of catalytic amounts of PdI_2/KI, CO, and O_2. In this latter case, the use of an excess of

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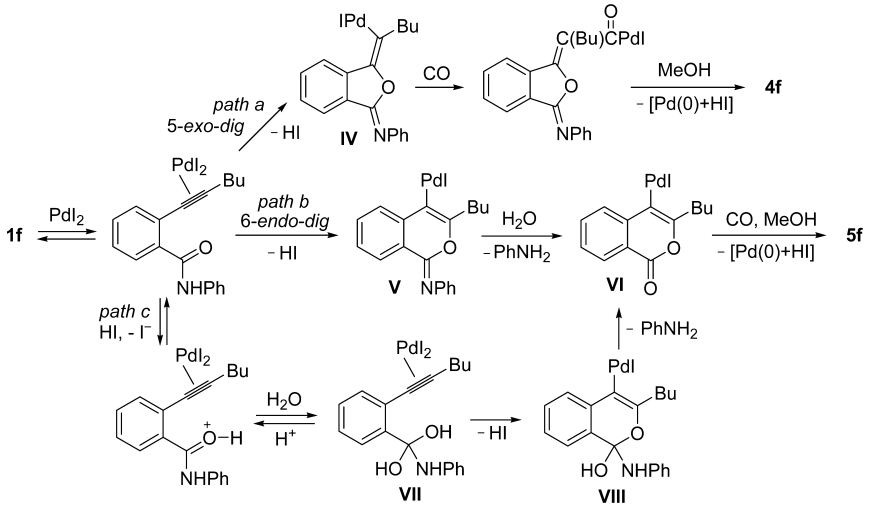
Scheme 4. Proposed Reaction Pathways for the Formation of Methyl 2-[3-(Phenylimino)isobenzofuran-1(3*H*)-ylidene]hexanoate 4f and Methyl 3-Butyl-1-oxo-1*H*-isochromene-4-carboxylate 5f from 2-(Hex-1-ynyl)-*N*-phenylbenzamide 1f



$HC(OR)_3$ as a dehydrating agent was essential for the success of the reaction, its function being to avoid the nucleophilic attack of water to the amide carbonyl of the substrate, which would favor the formation of 1-oxo-1*H*-isochromene-4-carboxylate esters **5** as side products.

EXPERIMENTAL SECTION

General Experimental Methods. Melting points are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded at 25 °C in $CDCl_3$ or DMSO-d_6 solutions at 300 or 500 MHz and 75 or 126 MHz, respectively, with Me_4Si as internal standard. Chemical shifts (δ) and coupling constants (J) are given in ppm and hertz, respectively. IR spectra were taken with an FT-IR spectrometer. Mass spectra were obtained using a GC–MS apparatus at 70 eV ionization voltage. Microanalyses were carried out at our analytical laboratory. All reactions were analyzed by TLC on silica gel 60 F_{254} or on neutral alumina and by GLC using a gas chromatograph and capillary columns with polymethylsilicone + 5% phenylsilicone as the stationary phase. Column chromatography was performed on silica gel 60 (70–230 mesh). Evaporation refers to the removal of solvent under reduced pressure.

Preparation of Substrates. 2-Alkynylbenzamides **1a–d,f–k** were prepared by coupling between the corresponding 2-iodobenzamide and the suitable terminal alkyne, followed (in the case of trimethylsilylacetylene) by deprotection, as described below. 2-Ethynylbenzamide **1e** was prepared in a similar manner from 2-bromobenzamide according to a literature procedure.[16] All other materials were commercially available and were used without further purification.

General Procedure for the Preparation of *N*-Substituted 2-Alkynylbenzamides 1a–d,f–k. *First Step: Preparation of 2-Iodobenzamides.* The method of Kundu and Khan[17] was employed. To a stirred solution of 2-iodobenzoyl chloride[18] (4.4 g, 16.5 mmol) in anhydrous benzene (43 mL) was slowly added, under nitrogen and dropwise, a solution of RNH_2 (33.3 mmol; R = Bu, 2.44 g; R = Bn, 3.57 g; R = Ph, 3.10 g; R = *t*-Bu, 2.44 g) in anhydrous benzene (15 mL). The resulting mixture was taken up with Et_2O (100 mL) and transferred in a separatory funnel. Aqueous HCl (1 M, 70 mL) was added, and the organic layer was separated and washed again with 1 M HCl (2 × 70 mL), satd Na_2CO_3 (3 × 70 mL), and water (3 × 70 mL). After drying over Na_2SO_4, the solvent was evaporated, and the crude 2-iodobenzamide thus obtained used as such for the next step.

Second Step: Sonogashira Coupling To Give N-Substituted 2-[(2-Trimethylsilyl)ethynyl)]benzamides and 2-Alkynylbenzamides 1f–k. The method of Kundu and Khan[17] was employed. A mixture of the crude 2-iodobenzamide (obtained as described above, formally corresponding to 16.5 mmol), $(Ph_3P)_2PdCl_2$ (405 mg, 0.58 mmol), CuI (251 mg, 1.32 mmol), and Et_3N (6.7 g, 66 mmol) in anhydrous DMF (82 mL) was stirred under nitrogen for 1 h. The 1-alkyne (19.8 mmol; trimethylsilylacetylene, 1.95 g; 1-hexyne, 1.63 g; phenylacetylene, 2.02 g; 1-ethynylcyclohex-1-ene, 2.10 g) was added under nitrogen, and the resulting mixture allowed to stir at 80–85 °C for 15 h. After cooling, CH_2Cl_2 was added (100 mL) followed by water (70 mL). The phases were separated, and the organic layer was washed with water (2 × 70 mL). After drying over Na_2SO_4, the product was purified by column chromatography on silica gel using as eluent 9:1 hexane–AcOEt (*N*-phenyl-2-[2-(trimethylsilyl)ethynyl]benzamide, *N*-benzyl-2-[2-(trimethylsilyl)ethynyl]benzamide, **1f**, **1g**, **1h**, **1i**, **1j**, **1k**), or 8:2 hexane–AcOEt (*N*-butyl-2-[2-(trimethylsilyl)ethynyl]-benzamide, *N*-*tert*-butyl-2-[2-(trimethylsilyl)ethynyl]benzamide).

N-Butyl-2-[2-(trimethylsilyl)ethynyl]benzamide:[3k] yield 2.66 g, starting from crude *N*-butyl-2-iodobenzamide and trimethylsilylacetylene (59%); yellow oil; IR (film) ν = 3391 (w, br), 3304 (m, br), 2959 (m), 2157 (m), 1648 (m), 1536 (m), 1475 (w), 1304 (m), 1250 (m), 872 (m), 844 (s), 758 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.12–8.08 (m, 1 H), 7.68 (s, br, 1 H), 7.53 (dd, J = 7.3, 1.2, 1 H), 7.47–7.36 (m, 2 H), 3.53–3.45 (m, 2 H), 1.63 (quintuplet, J = 7.3, 2 H), 1.44 (sextuplet, J = 7.3, 2 H), 0.97 (t, J = 7.3, 3 H), 0.29 (s, 9 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 166.0, 135.7, 134.2, 130.5, 130.4, 129.3, 119.4, 103.9, 101.7, 40.1, 31.9, 20.6, 14.0, 0.00; GC–MS m/z = 273 (4) [M$^+$], 272 (5), 258 (22), 244 (7), 230 (15), 217 (31), 202 (73), 201 (80), 187 (100), 172 (7), 161 (13), 145 (17), 143 (26), 128 (12), 115 (8), 93 (23), 75 (22). Anal. Calcd for $C_{16}H_{23}NOSi$ (273.45): C, 70.28; H, 8.48; N, 5.12; Si, 10.27. Found: C, 70.32; H, 8.45; N, 5.14; Si, 10.31.

N-Benzyl-2-[2-(trimethylsilyl]ethynyl]benzamide:[19] yield 2.98 g, starting from crude *N*-benzyl-2-iodobenzamide and trimethylsilylacetylene (59%); yellow solid; mp 80–82 °C; IR (KBr) ν = 3383 (m), 3299 (w), 2154 (m), 1652 (s), 1533 (m), 1296 (m), 1250 (m), 866 (s), 844 (s), cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.23–8.10 (m, 2 H, 1 H), 7.60–7.49 (m, 1 H), 7.48–7.23 (m, 7 H), 4.67 (d, J = 5.5, 2 H), 0.11 (s, 9 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 165.7, 138.0, 134.8, 134.1, 130.6, 130.4, 129.2, 128.7, 127.8, 127.5, 119.4, 103.6, 102.1, 44.1, −0.5; GC–MS m/z = 307 (32) [M$^+$], 306 (47), 292 (19), 290 (22), 276 (5), 234 (20), 216 (22), 201 (27), 187 (91), 159 (14), 143 (17), 129 (11), 106 (11), 91 (100), 75 (27), 73 (42). Anal. Calcd for $C_{19}H_{21}NOSi$ (307.46): C, 74.22; H, 6.88; N, 4.56; Si, 9.13. Found: C, 74.19; H, 6.85; N, 4.59; Si, 9.12.

N-Phenyl-2-[2-(trimethylsilyl)ethynyl]benzamide: yield 3.20 g, starting from crude 2-iodo-*N*-phenylbenzamide and trimethylsilylacetylene (66%); yellow solid; mp 97–98 °C (lit.[17] mp 95–96 °C, lit.[20] mp 96–97 °C); IR (KBr) ν = 3303 (m, br), 2959 (w), 2157 (m), 1660 (s), 1601 (m), 1541 (s), 1500 (m), 1447 (m), 1323 (m), 1250 (m),

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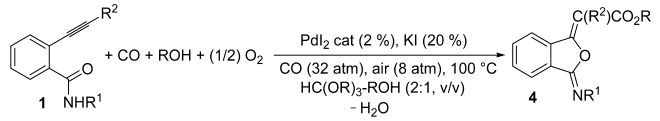
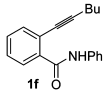
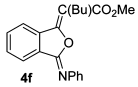
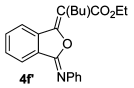
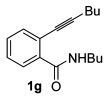
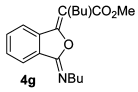
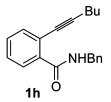
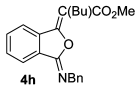
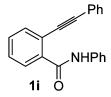
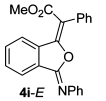
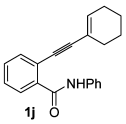
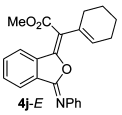
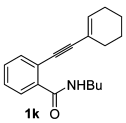
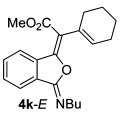
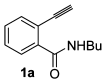
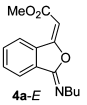
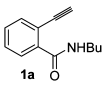
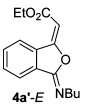
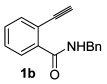
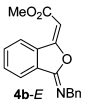
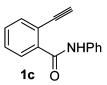
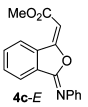
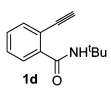
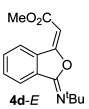
Table 2. Synthesis of 3-[(Alkoxycarbonyl)methylene]isobenzofuran-1(3*H*)-imines 4 by PdI_2-Catalyzed *O*-Heterocyclization–Alkoxycarbonylation of 2-Alkynylbenzamides 1[a]



entry	1	R^1	R^2	R	time (h)	4	yield of 4[b] (%)
1	 **1f**	Ph	Bu	Me	8	 **4f**	80[c]
2	**1f**	Ph	Bu	Et	15	 **4f'**	83[d]
3	 **1g**	Bu	Bu	Me	5	 **4g**	75[e]
4	 **1h**	Bn	Bu	Me	15	 **4h**	45[f]
5	 **1i**	Ph	Ph	Me	15	 **4i-*E***	55[g]
6	 **1j**	Ph	1-cyclohexyl	Me	5	 **4j-*E***	78[h]
7	 **1k**	Bu	1-cyclohexyl	Me	5	 **4k-*E***	68[h]
8	 **1a**	Bu	H	Me	5	 **4a-*E***	70[h]
9	 **1a**	Bu	H	Et	5	 **4a'-*E***	70[h]
10	 **1b**	Bn	H	Me	8	 **4b-*E***	60[h]
11	 **1c**	Ph	H	Me	5	 **4c-*E***	58[h]
12	 **1d**	*t*-Bu	H	Me	5	 **4d-*E***	70[i]

[a]All reactions were carried out in a $HC(OR)_3$–ROH mixture (2:1, v/v) as the solvent (concentration of **1** = 0.02 mmol per mL of solvent) at 100 °C and under 40 atm (at 25 °C) of a 4:1 mixture of CO–air, in the presence of 2 mol % of PdI_2 in conjunction with an excess of KI (KI/PdI_2 molar ratio = 10). Conversion of **1** was quantitative in all cases. [b]Isolated yield based on starting **1**. [c]*Z*/*E* ratio = 1.4 (determined by ^{1}H NMR). [d]*Z*/*E* ratio ca. 1:1 (determined by ^{1}H NMR). [e]*E*/*Z* ratio = 6.2 (determined by ^{1}H NMR). [f]*E*/*Z* ratio = 4.9 (determined by ^{1}H NMR). [g]The reaction was selective toward the formation of the *E* isomer. The structure of **4i**-*E* was confirmed by X-ray diffraction analysis. [h]The reaction was selective toward the formation of the *E* isomer. [i]The reaction was selective toward the formation of the *E* isomer. The structure of **4d**-*E* was confirmed by X-ray diffraction analysis.

dx.doi.org/10.1021/jo500281h | *J. Org. Chem.* 2014, 79, 3506–3518

868 (s), 844 (s), 756 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 9.29 (s, br, 1 H), 8.13−8.09 (m, 1 H), 7.68 (d, J = 7.9, 2 H), 7.60−7.55 (m, 1 H), 7.48−7.40 (m, 2 H), 7.37 (t, J = 7.9, 2 H), 7.18−7.12 (t, J = 7.3, 1 H), 0.23 (s, 9 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 164.1, 138.0, 136.0, 134.0, 130.8, 130.3, 129.3, 129.0, 124.5, 120.3, 119.5, 103.1, 102.8, −0.18; GC−MS m/z = 293 (11) [M^+], 278 (5), 219 (6), 201 (100), 161 (7), 145 (12), 143 (9), 117 (5). Anal. Calcd for $C_{18}H_{19}NOSi$ (293.44): C, 73.68; H, 6.53; N, 4.77; Si, 9.57. Found: C, 73.62; H, 6.50; N, 4.78; Si, 9.62.

N-tert-Butyl-2-[2-(trimethylsilyl)ethynyl]benzamide: yield 2.25 g, starting from crude *N-tert*-butyl-2-iodobenzamide (50%) and trimethylsilylacetylene; yellow solid mp 58−59 °C; IR (KBr) ν = 3293 (m, br), 2962 (m), 2161 (m), 1643 (s), 1598 (w), 1539 (s), 1478 (w), 1447 (w), 1362 (w), 1324 (m), 1249 (m), 1222 (m), 842 (s), 753 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 7.96 (d, J = 7.3, 1 H), 7.50 (d, J = 7.3, 1 H), 7.43−7.31 (m, 2 H), 7.22 (s, br, 1 H), 1.49 (s, 9 H), 0.28 (s, 9 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 165.5, 137.1, 134.3, 130.0, 129.7, 129.1, 119.3, 103.6, 101.3, 52.1, 28.9, 0.0; GC−MS m/z = 273 (3) [M^+], 258 (4), 217 (67), 202 (100), 184 (24), 161 (5), 145 (12), 143 (24), 121 (15), 75 (20). Anal. Calcd for $C_{16}H_{23}NOSi$ (273.45): C, 70.28; H, 8.48; N, 5.12; Si, 10.27. Found: C, 70.30; H, 8.44; N, 5.16; Si, 10.24.

*2-(Hex-1-ynyl)-N-phenylbenzamide (**1f**):* yield 3.20 g, starting from crude 2-iodo-*N*-phenylbenzamide and 1-hexyne (70%); yellow solid; mp 56−57 °C; IR (KBr) ν = 3467 (m, br), 3315 (s), 2959 (w), 2927 (m), 2858 (w), 2225 (vw), 1664 (s), 1597 (m), 1524 (m), 1436 (m), 1322 (m), 892 (w), 756 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 9.40 (s, br, 1 H), 8.13−8.00 (m, 1 H), 7.66 (d, J = 7.9, 1 H), 7.53−7.43 (m, 1 H), 7.43−7.27 (m, 5 H), 7.12 (t, J = 7.3, 1 H), 2.49 (t, J = 7.0, 2 H), 1.64−1.50 (m, 2 H), 1.50−1.34 (m, 2 H), 0.87 (t, J = 7.0, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 164.5, 138.1, 135.6, 133.7, 130.7, 130.1, 129.0, 128.3, 124.4, 120.3, 120.1, 98.4, 79.2, 30.6, 22.1, 19.4, 13.5; GC−MS m/z = 277 (100) [M^+], 262 (4), 248 (38), 235 (86), 185 (89), 167 (11), 143 (39), 128 (18), 115 (51). Anal. Calcd for $C_{19}H_{19}NO$ (277.36): C, 82.28; H, 6.90; N, 5.05. Found: C, 82.30; H, 6.88; N, 5.07 .

*N-Butyl-2-(hex-1-ynyl)benzamide (**1g**):* yield 2.84 g, starting from crude *N*-butyl-2-iodo-benzamide and 1-hexyne (67%); yellow solid; mp 52−54 °C (lit.[21] mp 57−60 °C); IR (KBr) ν = 3278 (m, br), 2953 (m), 2935 (m), 2861 (w), 2225 (vw), 1649 (s), 1548 (m), 1469 (w), 1435 (m), 1313 (m), 763 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 8.14−8.04 (m, 1 H), 7.63 (s, br, 1 H), 7.54−7.46 (m, 1 H), 7.45−7.36 (m, 2 H), 3.52 (q, J = 6.7, 2 H), 2.51 (t, J = 6.7, 2 H), 1.78−1.60 (m, 4 H), 1.59−1.45 (m, 4 H), 1.00 (t, J = 7.3, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 166.3, 135.4, 133.7, 130.2, 130.0, 128.1, 120.2, 97.2, 79.6, 39.8, 31.7, 30.6, 22.1, 20.3, 19.4, 13.8, 13.6; GC−MS m/z = 257 (99) [M^+], 242 (10), 228 (77), 215 (100), 200 (18), 185 (33), 172 (54), 158 (52), 143 (25), 128 (21), 115 (51), 103 (8), 77 (8). Anal. Calcd for $C_{17}H_{23}NO$ (257.37): C, 79.33; H, 9.01; N, 5.44. Found: C, 79.30; H, 9.02; N, 5.41.

*N-Benzyl-2-(hex-1-ynyl)benzamide (**1h**):*[19] yield 3.27 g, starting from crude *N*-benzyl-2-iodobenzamide and 1-hexyne (68%); yellow solid; mp 40−41 °C; IR (KBr) ν = 3378 (m, br), 3311 (m, br), 2956 (m), 2935 (m), 2871 (w), 2227 (vw), 1651 (s), 1595 (w), 1531 (s), 1455 (w), 1298 (m), 1154 (w), 757 (m), 699 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 8.16−8.08 (m, 1 H), 8.04 (s, br, 1 H), 7.48−7.22 (m, 8 H), 4.66 (d, J = 5.4, 2 H), 2.14 (t, J = 6.8, 2 H), 1.45−1.23 (m, 4 H), 0.86 (t, J = 7.0, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 166.0, 138.1, 134.7, 133.6, 130.5, 130.2, 128.7, 128.1, 128.0, 127.5, 120.3, 97.8, 79.5, 44.3, 30.3, 22.1, 19.1, 13.5; GC−MS m/z = 291 (9) [M^+], 262 (5), 249 (42), 231 (8), 200 (92), 182 (9), 172 (11), 158 (65), 143 (11), 132 (18), 115 (38), 91 (100). Anal. Calcd for $C_{20}H_{21}NO$ (291.39): C, 82.44; H, 7.26; N, 4.81. Found: C, 82.47; H, 7.23; N, 4.84.

*N-Phenyl-2-(2-phenylethynyl)benzamide (**1i**):* yield 2.83 g, starting from crude *N*-phenyl-2-iodobenzamide and phenylacetylene (58%); white solid; mp 153−154 °C (lit.[22] mp 151−153 °C); IR (KBr) ν = 3277 (s), 3056 (w), 2217 (vw), 1654 (s), 1594 (m), 1524 (s), 1440 (m), 1323 (m), 921 (w), 889 (w), 759 (s), 687 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 9.20 (s, br, 1 H), 8.20−8.12 (m, 1 H), 7.72−7.60 (m, 3 H), 7.54−7.46 (m, 4 H), 7.44−7.30 (m, 5 H), 7.20−7.10 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 164.4, 138.1, 136.1, 133.5, 131.7, 130.8, 130.3, 129.5, 129.3, 129.1, 128.6, 124.5, 122.0, 120.1, 119.7, 96.6, 87.3; GC−MS m/z = 297 (26) [M^+], 269 (9), 268 (11), 205 (100), 177 (21), 176 (45), 151 (17). Anal. Calcd for $C_{21}H_{15}NO$ (297.35): C, 84.82; H, 5.08; N, 4.71. Found: C, 84.80; H, 5.05; N, 4.70.

*2-(2-Cyclohexenylethynyl)-N-phenylbenzamide (**1j**):* yield 3.28 g, starting from crude 2-iodo-*N*-phenylbenzamide and 1-ethynylcyclohex-1-ene (66%); yellow solid; mp 97−98 °C (lit.[8e] mp 99−100 °C); IR (KBr) ν = 3450 (m, br), 3299 (m), 2929 (s), 2858 (m), 2200 (vw), 1667 (vs), 1601 (w), 1539 (m), 1496 (m), 1440 (m), 1386 (m), 1323 (m), 1255 (m), 1094 (m), 759 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 9.33 (s, br, 1 H), 8.17−8.09 (m, 1 H), 7.69 (d, J = 7.7, 2 H), 7.55−7.48 (m, 1 H), 7.46−7.32 (m, 4 H), 7.19−7.10 (m, 1 H), 6.31−6.22 (m, 1 H), 2.27−2.07 (m, 4 H), 1.72−1.52 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 164.3, 138.1, 137.5, 135.4, 133.5, 130.8, 130.4, 129.0, 128.6, 124.4, 119.9, 98.9, 84.9, 29.0, 25.9, 22.2, 21.4; GC−MS m/z = 301 (54) [M^+], 272 (5), 209 (100), 194 (8), 178 (9), 165 (34), 152 (17), 143 (12), 139 (7), 115 (10). Anal. Calcd for $C_{21}H_{19}NO$ (301.38): C, 83.69; H, 6.35; N, 4.65. Found: C, 83.70; H, 6.36; N, 4.62.

*N-Butyl-2-(2-cyclohexenylethynyl)benzamide (**1k**):* yield 2.69 g, starting from crude *N*-butyl-2-iodo-benzamide and 1-ethynylcyclohex-1-ene (58%); yellow solid; mp 89−90 °C; IR (KBr) ν = 3446 (m, br), 3286 (m), 2928 (m), 2858 (w), 2205 (vw), 1636 (s), 1566 (m), 1434 (m), 1311 (m), 1143 (w), 765 (m), 711 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 8.09−8.02 (m, 1 H), 7.47 (s, br, 1 H), 7.50−7.43 (m, 1 H), 7.41−7.33 (m, 2 H), 6.30−6.15 (m, 1 H), 3.53−3.44 (m, 2 H), 2.28−2.12 (m, 4 H), 1.78−1.54 (m, 6 H), 1.53−1.38 (m, 2 H), 0.95 (t, J = 7.3, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 166.2, 136.7, 135.3, 133.4, 130.2, 130.1, 128.3, 120.2, 120.0, 97.6, 85.3, 39.9, 31.7, 29.0, 25.9, 22.2, 21.4, 20.3, 13.8; GC−MS m/z = 281 (98) [M^+], 264 (15), 252 (22), 238 (46), 225 (54), 224 (50), 209 (86), 197 (86), 181 (49), 165 (100), 152 (56), 139 (22), 130 (29), 115 (33), 102 (15), 97 (12), 77 (20). Anal. Calcd for $C_{19}H_{23}NO$ (281.39): C, 81.10; H, 8.24; N, 4.98. Found: C, 81.08; H, 8.26; N, 4.97 .

*Deprotection Step To Give N-Substituted 2-Ethynylbenzamides **1a−d**.* To a solution of 2-[2-(trimethylsilyl)ethynyl]benzamide obtained as described above (5.14 mmol; *N*-butyl-2-[2-(trimethylsilyl)ethynyl]benzamide, 1.4 g; *N-tert*-butyl-2-[2-(trimethylsilyl)ethynyl]benzamide, 1.4 g; *N*-phenyl-2-[2-(trimethylsilyl)ethynyl]benzamide, 1.5 g; *N*-benzyl-2-[2-(trimethylsilyl)ethynyl]benzamide, 1.6 g) in MeOH (25 mL) was added KF (1.06 g, 18.2 mmol), and the resulting mixture was allowed to stir at room temperature for 2 h. The solvent was evaporated, and the residue was taken up with Et_2O (40 mL) and washed with water (40 mL). The aqueous layer was extracted with Et_2O (3 × 40 mL), and the collected organic phases were dried over $MgSO_4$. After filtration, the solvent was evaporated to give the *N*-substituted 2-ethynylbenzamide, which was sufficiently pure for the carbonylation reactions.

*N-Butyl-2-ethynylbenzamide (**1a**):* yield 0.941 g, starting from 1.40 g of *N*-butyl-2-[2-(trimethylsilyl)ethynyl]benzamide (91%); yellow solid; mp 53−54 °C (lit.[16] mp 58−60 °C); IR (KBr) ν = 3296 (s, br), 3253 (s, br), 2950 (m), 2869 (m), 2106 (vw), 1655 (s), 1547 (s), 1468 (m), 1351 (m), 1258 (m), 1151 (m), 1099 (w), 942 (w), 856 (w), 761 (m), 694 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 7.97−7.90 (m, 1 H), 7.57−7.52 (m, 1 H), 7.47−7.35 (m, 2 H), 6.88 (s, br, 1 H), 3.48 (s, 1 H), 3.47 (q, J = 6.6, 2 H), 1.68−1.55 (m, 2 H), 1.51−1.36 (m, 2 H), 0.95 (t, J = 7.3, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 166.2, 137.1, 134.0, 130.2, 129.7, 129.3, 118.4, 83.3, 82.3, 39.9, 31.4, 20.3, 13.7; GC−MS m/z = 201 (absent) [M^+], 200 (2), 186 (7), 172 (9), 159 (26), 158 (26), 146 (12), 145 (60), 130 (21), 129 (100), 102

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(11), 101 (45), 75 (18). Anal. Calcd for $C_{13}H_{15}NO$ (201.26): C, 77.58; H, 7.51; N, 6.96. Found: C, 77.61; H, 7.54; N, 6.97.

*N-Benzyl-2-ethynylbenzamide (**1b**):* yield 1.16 g, starting from 1.60 g of *N*-benzyl-2-[2-(trimethylsilyl]ethynyl]benzamide (96%); colorless solid; mp 87−88 °C; IR (KBr) ν = 3286 (s, br), 3062 (w), 2112 (vw), 1643 (s), 1543 (m), 1428 (w), 1310 (m), 1239 (w), 764 (m), 701 (m), 669 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 7.98−7.91 (m, 1 H), 7.55−7.20 (m, 9 H), 4.65 (d, *J* = 5.6, 2 H), 3.32 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 166.2, 137.9, 136.6, 134.0, 130.4, 129.7, 129.3, 128.6, 127.9, 127.5, 118.6, 83.6, 82.1, 44.3 ; GC−MS *m*/*z* = 235 (61) [M^+], 234 (79), 218 (67), 216 (27), 189 (30), 130 (25), 129 (69), 102 (54), 101 (100), 91 (72), 77 (24), 75 (47), 65 (24), 51 (33). Anal. Calcd for $C_{16}H_{13}NO$ (235.28): C, 81.68; H, 5.57; N, 5.95. Found: C, 81.65; H, 5.56; N, 5.98.

*2-Ethynyl-N-phenylbenzamide (**1c**):* yield 1.00 g, starting from 1.50 g of *N*-phenyl-2-[2-(trimethylsilyl)ethynyl]benzamide (88%); yellow solid; mp 94−97 °C (lit.[20] mp 95−98 °C); IR (KBr) ν = 3282 (s, br), 3130 (w), 2107 (vw), 1647 (s), 1596 (m), 1538 (m), 1491 (w), 1446 (m), 1326 (m), 1256 (w), 754 (m), 675 (m), 633 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 9.00 (s, br, 1 H), 8.07−8.02 (m, 1 H), 7.67 (d, *J* = 7.9, 2 H), 7.63−7.58 (m, 1 H), 7.51−7.43 (m, 2 H), 7.37 (t, *J* = 7.9, 2 H), 7.19−7.13 (m, 1 H), 3.59 (s, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 164.2, 138.0, 136.9, 134.2, 130.8, 130.1, 129.6, 129.1, 124.6, 120.1, 118.4, 84.3, 82.0; GC−MS *m*/*z* = 221 (99) [M^+], 220 (100), 193 (16), 178 (5), 165 (34), 152 (5), 130 (4), 102 (6), 95 (10), 77 (18), 51 (15). Anal. Calcd for $C_{15}H_{11}NO$ (221.25): C, 81.43; H, 5.01; N, 6.33. Found: C, 81.40; H, 5.02; N, 6.31.

*N-tert-Butyl-2-ethynylbenzamide (**1d**):* yield 0.88 g, starting from 1.40 g of *N*-*tert*-butyl-2-[2-(trimethylsilyl)ethynyl]benzamide (85%); yellow solid; mp 62.5−63.5 °C; IR (KBr) ν = 3260 (s, br), 3069 (m), 2966 (m), 2106 (vw), 1634 (s), 1550 (s), 1448 (m), 1391 (w), 1364 (m), 1227 (s), 953 (w), 877 (m), 754 (s), 654 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 7.95−7.89 (m, 1 H), 7.56−7.50 (m, 1 H), 7.46−7.33 (s, 2 H), 7.03 (s, br, 1 H), 3.49 (s, 1 H), 1.47 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 165.4, 138.1, 133.9, 130.0, 129.4, 129.3, 118.3, 83.4, 82.3, 52.1, 28.7; GC−MS *m*/*z* = 201 (2) [M^+], 186 (10), 158 (2), 145 (95), 129 (100), 117 (5), 101 (45), 75 (19). Anal. Calcd for $C_{13}H_{15}NO$ (201.26): C, 77.58; H, 7.51; N, 6.96. Found: C, 77.61; H, 7.54; N, 6.95.

General Procedure for the PdI_2-Catalyzed Aminocarbonylation−*N*-Heterocyclization of 2-Ethynylbenzamides 1a−e To Give Carbonylated Isoindolinone Derivatives 3 (Table 1). A 250 mL stainless steel autoclave was charged in the presence of air with PdI_2 (5.0 mg, 1.39 × 10^{-2} mmol), KI (23.0 mg, 1.39 × 10^{-1} mmol), and a solution of **1** [**1a** (141 mg), **1b** (165 mg), **1c** (155 mg), **1d** (141 mg), **1e** (102 mg); 0.70 mmol] in a 2:1 mixture MeCN−amine (MeCN: 9.4 mL; amine **2**: 4.6 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 the required time (see Table 1), the autoclave was cooled, degassed, and opened. When necessary, the mixture was filtered (to remove the solid oxamide byproduct deriving from double carbonylation of **2**) and the solid washed with cold Et_2O. The solvent was evaporated, and the products were purified by column chromatography on silica gel to give pure carbonylated isoindolinones **3** (eluent: chloroform for **3aa**; 7:3 hexane−AcOEt for **3ca**-*Z* and **3da**-*E*; 8:2 hexane−AcOEt for **3ea**-*Z*; 9:1 hexane−AcOEt for **3db**-*E*) or neutral alumina (eluent: 8:2 hexane−AcOEt for **3ba**; 7:3 hexane−AcOEt for **3ab** and **3ad**; 9:1 hexane−AcOEt for **3ac**; 99:1 hexane−AcOEt for **3dc**-*E*). In the case of **3aa**, **3ba**, **3ab**, and **3ac** an inseparable mixture of the *Z* and *E* diastereoisomers was obtained. In the case of **3ad**, it was possible to separate the *Z* and *E* isomers (order of elution: *E*, *Z*).

*2-Butyl-3-(2-morpholino-2-oxoethylidene)isoindolin-1-one (**3aa**):* yield 178.4 mg, starting from 141.0 mg of *N*-butyl-2-ethynylbenzamide (81%) (mixture of diastereoisomers *Z*/*E*, *Z*/*E* ratio ca. 2.0, determined by ^1H NMR); pale yellow oil; IR (film) ν = 2960 (m), 2928 (m), 1712 (s), 1684 (vs), 1435 (m), 1400 (w), 1231 (m), 1115 (m), 1040 (w), 769 (m), 699 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 8.12−8.01 [*Z* (m, 1 H)], 7.88−7.76 [*Z* (m, 1 H) + *E* (m, 1 H)], 7.70−7.46 [*Z* (m, 2 H) + *E* (m, 3 H)], 6.01 [*E* (s, 1 H)], 5.81 [*Z* (s, 1 H)], 4.02 [*E* (t, *J* = 7.5, 2 H)], 3.88−3.55 [*Z* (m, 10 H) + *E* (m, 8 H)], 1.73−1.58 [*Z* (m, 2 H)], 1.58−1.23 [*E* (m, 4 H) + *Z* (m, 2 H)], 1.01−0.88 [*Z* (m, 3 H) + *E* (m, 3 H)]; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 168.1, 166.7, 165.3, 164.8, 142.2, 139.9, 137.2, 134.0, 132.5, 132.2, 130.4, 130.14, 130.07, 128.4, 124.7, 123.4, 123.1, 119.5, 99.5, 96.4, 66.8, 66.7, 66.6, 47.2, 47.1, 42.1, 41.9, 40.7, 39.2, 30.7, 30.3, 20.2, 20.0, 13.9, 13.8; GC−MS *m*/*z* = 314 (12) [M^+], 271 (5), 228 (100), 210 (11), 200 (48), 186 (11), 172 (32), 159 (12), 158 (12), 146 (6), 130 (34), 114 (4), 102 (8), 89 (7). Anal. Calcd for $C_{18}H_{22}N_2O_3$ (314.38): C, 68.77; H, 7.05; N, 8.91. Found: C, 68.80; H, 7.04; N, 8.89.

*2-Benzyl-3-(2-morpholino-2-oxoethylidene)isoindolin-1-one (**3ba**):* yield 202.7 mg, starting from 165.0 mg of *N*-benzyl-2-ethynylbenzamide (83%) (mixture of diastereoisomers *Z*/*E*, *Z*/*E* ratio ca. 2.2, determined by ^1H NMR); colorless solid; mp 95−96 °C; IR (KBr) ν = 3441 (m, br), 2964 (w), 2922 (m), 2856 (w), 1714 (s), 1647 (s), 1433 (m), 1272 (w), 1233 (w), 1115 (m), 968 (w), 696 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 8.19−8.11 [*Z* (m, 1 H) + *E* (m, 1 H)], 7.97−7.88 [*Z* (m, 1 H) + *E* (m, 1 H)], 7.70−7.51 [*Z* (m, 2 H) + *E* (m, 2 H)], 7.38−7.18 [*Z* (m, 4 H) + *E* (m, 4 H)], 7.09−7.00 [*Z* (m, 1 H) + *E* (m, 1 H)], 5.94 [*E* (s, 1 H)], 5.63 [*Z* (s, 1 H)], 5.35 [*E* (s, 2 H)], 5.04 [*Z* (s, 2 H)], 3.79−3.53 [*Z* (m, 6 H) + *E* (m, 6 H)], 3.53−3.32 [*Z* (m, 2 H) + *E* (m, 2 H)]; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 168.3, 166.9, 164.8, 164.3, 160.9, 141.6, 139.7, 137.32, 137.28, 136.4, 134.0, 132.8, 132.5, 130.6, 130.3, 129.8, 128.9, 128.6, 128.5, 127.7, 127.6, 127.2, 126.9, 126.7, 126.4, 125.2, 123.9, 123.5, 119.6, 66.7, 66.6, 66.2, 65.9, 47.2, 46.7, 43.8, 43.3; GC−MS *m*/*z* = 348 (17) [M^+], 262 (100), 234 (35), 172 (3), 91 (98), 65 (10). Anal. Calcd for $C_{21}H_{20}N_2O_3$ (348.40): C, 72.40; H, 5.79; N, 8.04. Found: C, 72.38; H, 5.81; N, 8.07.

*(Z)-3-(2-Morpholino-2-oxoethylidene)-2-phenylisoindolin-1-one (**3ca**-Z):* yield 201.6 mg, starting from 155.0 mg of 2-ethynyl-*N*-phenylbenzamide (86%); yellow solid; mp 133−134 °C; IR (KBr) ν = 3010 (w), 2969 (m), 2923 (m), 2856 (w), 1716 (s), 1652 (m), 1500 (w), 1472 (w), 1392 (m), 1237 (m), 1117 (m), 1043 (m), 979 (w), 753 (s), 699 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 8.24−8.18 (m, 1 H), 7.98−7.92 (m, 1 H), 7.70−7.41 (m, 5 H), 7.39−7.32 (m, 2 H), 5.64 (s, 1 H), 3.81−3.69 (m, 4 H), 3.64−3.56 (m, 2 H), 3.47−3.38 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 166.4, 165.2, 144.2, 134.0, 133.9, 133.0, 130.9, 129.8, 128.9, 128.7, 125.1, 123.7, 101.4, 66.8, 47.0, 42.1; GC−MS *m*/*z* = 334 (7) [M^+], 248 (100), 221 (11), 202 (3), 191 (7), 165 (23), 101 (3), 89 (3), 77 (10). Anal. Calcd for $C_{20}H_{18}N_2O_3$ (334.37): C, 71.84; H, 5.43; N, 8.38. Found: C, 71.86; H, 5.43; N, 8.36.

*(E)-2-tert-Butyl-3-(2-morpholino-2-oxoethylidene)isoindolin-1-one (**3da**-E):* yield 205.0 mg, starting from 141.0 mg of *N*-*tert*-butyl-2-ethynylbenzamide (93%); colorless solid; mp 145−146 °C; IR (KBr) ν = 2979 (w), 2954 (w), 2855 (w), 1708 (s), 1637 (vs), 1433 (m), 1374 (w), 1301 (w), 1232 (m), 1115 (m), 1020 (w), 772 (m), 699 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 7.79−7.71 (m, 2 H), 7.56−7.43 (m, 2 H), 6.14 (s, 1 H), 3.86−3.52 (m, 8 H), 1.78 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 166.1, 160.9, 141.0, 134.4, 132.3, 130.0, 128.1, 122.99, 122.97, 104.5, 67.3, 66.5, 57.8, 42.1, 40.7, 30.3; GC−MS *m*/*z* = 314 (6) [M^+], 258 (3), 228 (2), 200 (10), 172 (100), 145 (13), 130 (28), 114 (8), 102 (6), 86 (22). Anal. Calcd for $C_{18}H_{22}N_2O_3$ (314.38): C, 68.77; H, 7.05; N, 8.91. Found: C, 68.80; H, 7.03; N, 8.90.

*(Z)-3-(2-Morpholino-2-oxoethylidene)isoindolin-1-one (**3ea**-Z):* yield 117.7 mg, starting from 102.0 mg of 2-ethynylbenzamide (65%); colorless solid; mp 186−187 °C; IR (KBr) ν = 3412 (s, br), 1711 (s), 1647 (s), 1583 (w), 1399 (m), 1238 (m), 1120 (m), 758 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 10.34 (s, br, 1 H), 7.90−7.83 (s, 1 H), 7.73−7.65 (m, 1 H), 7.64−7.54 (m, 2 H), 6.06 (s, 1 H), 3.83−3.55 (m, 8 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 168.2, 166.0, 146.7, 137.0, 132.5, 131.2, 131.0, 129.7, 124.0, 120.5, 89.0, 66.9, 46.9, 45.8; GC−MS *m*/*z* = 258 (22) [M^+], 172 (100), 145 (16), 130 (45), 102 (15), 89 (28), 86 (41). Anal. Calcd for $C_{14}H_{14}N_2O_3$ (258.27): C, 65.11; H, 5.46; N, 10.85. Found: C, 65.10; H, 5.45; N, 10.87.

*2-Butyl-3-[2-oxo-2-(piperidin-1-yl)ethylidene]isoindolin-1-one (**3ab**):* yield 197.1 mg, starting from 141.0 mg of *N*-butyl-2-ethynylbenzamide (90%) (mixture of diastereoisomers *Z*/*E*, *Z*/*E*

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ratio ca. 1.0, determined by ^{1}H NMR); pale yellow oil; IR (film) ν = 2934 (m), 2956 (m), 1713 (s), 1652 (vs), 1470 (m), 1252 (m), 1023 (m), 953 (w), 770 (m), 698 (w) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.03−7.96 [*Z* (m, 1 H)], 7.86−7.77 [*Z* (m, 1 H) + *E* (m, 1 H)], 7.69−7.62 [*E* (m, 1 H)], 7.61−7.46 [*Z* (m, 2 H) + *E* (m, 2 H)], 6.04 [*E* (s, 1 H)], 5.83 [*Z* (s, 1 H)], 3.99 [*E* (t, *J* = 7.6, 2 H)], 3.83−3.49 [*Z* (m, 6 H) + *E* (m, 4 H)], 1.75−1.24 [*E* (m, 10 H) + *Z* (m, 10 H)], 0.96 [*Z* or *E* (t, *J* = 7.3, 3 H)], 0.92 [*Z* or *E* (t, *J* = 7.3, 3 H)]; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 168.1, 166.8, 165.0, 164.5, 140.9, 138.7, 137.4, 134.3, 132.3, 132.0, 130.1, 129.9, 124.5, 123.3, 123.1, 119.4, 111.7, 109.4, 101.0, 97.9, 48.0, 47.9, 42.8, 42.5, 40.7, 39.2, 30.7, 30.4, 26.7, 26.4, 25.8, 25.5, 24.58, 24.53, 20.2, 20.1, 13.82, 13.78; GC−MS *m*/*z* = 312 (35) [M$^+$], 283 (3), 269 (13), 239 (8), 228 (100), 210 (17), 201 (59), 200 (69), 186 (30), 172 (56), 159 (67), 146 (13), 130 (69), 112 (11), 102 (18), 84 (72). Anal. Calcd for $C_{19}H_{24}N_2O_2$ (312.41): C, 73.05; H, 7.74; N, 8.97. Found: C, 73.07; H, 7.71; N, 8.94.

*(E)-2-tert-Butyl-3-[2-oxo-2-(piperidin-1-yl)ethylidene]isoindolin-1-one (**3db**-E):* yield 166.2 mg, starting from 141.0 mg of *N*-*tert*-butyl-2-ethynylbenzamide (76%); colorless solid; mp 135−136 °C; IR (KBr) ν = 3446 (m, br), 2987 (m), 2938 (m), 2857 (w), 2257 (m), 1713 (m), 1634 (s), 1443 (m), 1373 (m), 1232 (m), 1110 (m), 1023 (m), 756 (m), 696 (m) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.80−7.70 (m, 2 H), 7.55−7.40 (m, 2 H), 6.19 (s, 1 H), 3.85−3.70 (m, 2 H), 3.57−3.42 (m, 2 H), 1.78 (s, 9 H), 1.74−1.60 (m, 4 H), 1.60−1.40 (m, 2 H)]; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 167.8, 165.6, 139.9, 134.6, 132.1, 130.6, 129.6, 123.1, 122.8, 106.0, 57.7, 48.0, 42.6, 30.4, 26.7, 25.5, 24.6; GC−MS *m*/*z* = 312 (17) [M$^+$], 256 (10), 255 (10), 200 (55), 172 (100), 145 (22), 130 (30), 112 (11), 84 (80). Anal. Calcd for $C_{19}H_{24}N_2O_2$ (312.41): C, 73.05; H, 7.74; N, 8.97. Found: C, 73.04; H, 7.72; N, 8.99.

*2-Butyl-3-[2-oxo-2-(pyrrolidin-1-yl)ethylidene]isoindolin-1-one (**3ac**):* yield 180.0 mg, starting from 141.0 mg of *N*-butyl-2-ethynylbenzamide (86%) (mixture of diastereoisomers *Z*/*E*, *Z*/*E* ratio ca. 1.8, determined by ^{1}H NMR); yellow oil; IR (film) ν = 2952 (m), 2915 (w), 2871 (m), 1712 (s), 1652 (s), 1616 (s), 1432 (m), 1398 (m), 1346 (m), 1190 (w), 1092 (w), 943 (w), 768 (m), 696 (m) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.61−8.53 [*Z* (m, 1 H) + *E* (m, 1 H)], 7.89−7.78 [*Z* (m, 1 H) + *E* (m, 1 H)], 7.64−7.48 [*Z* (m, 2 H) + *E* (m, 2 H)], 6.01 [*E* (s, 1 H)], 5.83 [*Z* (s, 1 H)], 4.15−4.01 [*E* (m, 2 H)], 3.81−3.71 [*Z* (m, 2 H)], 3.60−3.35 [*Z* (m, 4 H) + *E* (m, 4 H)], 2.10−1.62 [*Z* (m, 4 H) + *E* (m, 4 H)], 1.50−1.11 [*Z* (m, 4 H) + *E* (m, 4 H)], 1.10−0.80 [*Z* (m, 3 H) + *E* (m, 3 H)]; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 168.3, 167.1, 164.5, 164.4, 142.8, 138.9, 137.6, 134.2, 132.6, 132.1, 130.4, 130.1, 130.0, 128.6, 126.2, 123.4, 122.9, 119.4, 101.2, 98.3, 47.8, 47.6, 46.0, 45.8, 40.9, 39.2, 30.1, 29.7, 26.2, 26.1, 24.6, 24.5, 20.2, 20.0, 13.9, 13.8.; GC−MS *m*/*z* = 298 (23) [M$^+$], 255 (24), 228 (100), 200 (50), 186 (10), 172 (33), 158 (12), 130 (32), 102 (11), 70 (16), 55 (11). Anal. Calcd for $C_{18}H_{22}N_2O_2$ (298.38): C, 72.46; H, 7.43; N, 9.39. Found: C, 72.49; H, 7.42; N, 9.38 .

*(E)-2-tert-Butyl-3-[2-oxo-2-(pyrrolidin-1-yl)ethylidene]isoindolin-1-one (**3dc**-E):* yield 171.6 mg, starting from 141.0 mg of *N*-*tert*-butyl-2-ethynylbenzamide (82%); yellow oil; IR (film) ν = 2970 (w), 2875 (w), 1709 (s), 1631 (s), 1614 (s), 1434 (m), 1367 (m), 1298 (w), 1266 (w), 1112 (w), 1023 (w), 1006 (w), 797 (m), 693 (w) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.05−7.91 (m, 1 H), 7.81−7.65 (m, 1 H), 7.60−7.45 (m, 2 H), 6.23 (s, 1 H), 3.70−3.52 (m, 2 H), 3.51−3.40 (m, 2 H), 2.05−1.85 (m, 4 H), 1.79 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 165.3, 163.2, 141.0, 132.3, 129.8, 128.9, 125.8, 123.6, 122.7, 106.5, 47.6, 45.8, 30.4, 28.7, 26.1, 24.5; GC−MS *m*/*z* = 298 (17) [M$^+$], 242 (7), 200 (46), 172 (100), 145 (14), 130 (27), 98 (12), 89 (10), 70 (51). Anal. Calcd for $C_{18}H_{22}N_2O_2$ (298.38): C, 72.46; H, 7.43; N, 9.39. Found: C, 72.48; H, 7.44; N, 9.37.

*(Z)-N,N-Dibutyl-2-(2-butyl-3-oxoisoindolin-1-ylidene)acetamide (**3ad**-Z):* yield 120.0 mg, starting from 141.0 mg of *N*-butyl-2-ethynylbenzamide (48%); yellow oil; IR (film) ν = 2958 (m), 2931 (s), 2873 (m), 1714 (m), 1634 (s), 1532 (m), 1467 (m), 1091 (w) cm^{-1} ; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.21−8.15 (m, 1 H), 7.85−7.78 (m, 1 H), 7.61−7.46 (m, 2 H), 5.86 (s, 1 H), 3.61−3.05 (m, 6 H), 1.73−1.12 (m, 12 H), 1.05−0.62 (m, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 166.0, 157.8, 141.7, 138.7, 132.4, 130.2, 129.9, 125.3, 123.0, 101.1, 47.2, 40.6, 39.3, 32.6, 30.9, 20.3, 20.2, 20.1, 13.9, 13.85, 13.76; GC−MS *m*/*z* = 356 (20) [M$^+$], 327 (5), 313 (5), 299 (3), 228 (100), 210 (11), 201 (49), 186 (20), 172 (37), 159 (44), 146 (10), 130 (42), 102 (9). Anal. Calcd for $C_{22}H_{32}N_2O_2$ (356.50): C, 74.12; H, 9.05; N, 7.86. Found: C, 74.11; H, 9.07; N, 7.85.

*(E)-N,N-Dibutyl-2-(2-butyl-3-oxoisoindolin-1-ylidene)acetamide (**3ad**-E):* yield 119.7 mg, starting from 141.0 mg of *N*-butyl-2-ethynylbenzamide (48%); yellow oil; IR (film) ν = 2958 (m), 2931 (m), 2873 (m), 1716 (m), 1628 (s), 1533 (m), 1467 (m), 1376 (w), 1295 (w), 1219 (w), 1095 (w) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.81−7.75 (m, 1 H), 7.72−7.40 (m, 3 H), 6.04 (s, 1 H), 3.52−3.01 (m, 6 H), 2.72−1.15 (m, 12 H), 1.10−0.52 (m, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 165.6, 157.8, 139.0, 137.7, 132.1, 129.9, 125.5, 123.4, 119.3, 97.8, 47.1, 40.6, 32.6, 30.9, 20.4, 20.3, 13.88. 13.83; GC−MS *m*/*z* = 356 (19) [M$^+$], 327 (5), 313 (5), 228 (100), 210 (11), 201 (51), 186 (21), 172 (37), 159 (44), 146 (10), 130 (42), 102 (8). Anal. Calcd for $C_{22}H_{32}N_2O_2$ (356.50): C, 74.12; H, 9.05; N, 7.86. Found: C, 74.10; H, 9.06; N, 7.83.

General Procedure for the Synthesis of 3-[(Alkoxycarbonyl)-methylene]isobenzofuran-1(3*H*)imines 4 by PdI_2-Catalyzed *O*-Heterocyclization−Alkoxycarbonylation of 2-Alkynylbenzamides 1a−d and 1f−k (Table 2). A 250 mL stainless steel autoclave was charged in the presence of air with PdI_2 (5.0 mg, 1.39 × 10^{-2} mmol), KI (23.0 mg, 1.39 × 10^{-1} mmol), and a solution of **1** [**1a** (141 mg), **1b** (165 mg), **1c** (155 mg), **1d** (141 mg), **1f** (194 mg), **1g** (180 mg), **1h** (204 mg), **1i** (208 mg), **1j** (211 mg), **1k** (197 mg); 0.70 mmol] in a ROH/$HC(OR)_3$ mixture [R = Me, Et; ROH: 11.6 mL; $HC(OR)_3$: 23.1 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 the required time (see Table 2), the autoclave was cooled, degassed, and opened. The solvent was evaporated, and the products were purified by column chromatography on neutral alumina to give pure 3-[(alkoxycarbonyl)-methylene]isobenzofuran-1(3*H*)imines **4** (eluent: 95:5 hexane−AcOEt for **4a**-*E*, **4c**-*E*, **4d**-*E*, **4f**, **4f′**, **4g**, **4h**, **4i**-*E*, **4j**-*E*, and **4k**-*E*; 9:1 hexane−AcOEt for **4a′**-*E* and **4b**-*E*).

*(E)-Methyl 2-[3-(butylimino)isobenzofuran-1(3H)-ylidene]acetate (**4a**-E):* yield 127.3 mg, starting from 141.0 mg of *N*-butyl-2-ethynylbenzamide (70%); colorless solid; mp 106−107 °C; IR (KBr) ν = 2957 (m), 2932 (m), 2873 (w), 1687 (m), 1646 (s), 1582 (s), 1459 (m), 1402 (m), 1316 (w), 1221 (m), 1142 (m), 768 (m) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 9.09−9.00 (m, 1 H), 7.92−7.84 (m, 1 H), 7.68−7.56 (m, 2 H), 5.94 (s, 1 H), 3.80 (s, 3 H), 3.66 (t, *J* = 7.2, 2 H), 1.78−1.61 (m, 2 H), 1.52−1.37 (m, 2 H), 0.97 (t, *J* = 7.3, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 167.0, 161.8, 152.8, 133.7, 132.6, 132.1, 132.0, 127.7, 122.6, 96.6, 51.5, 47.9, 32.9, 20.6, 13.9; GC−MS *m*/*z* = 259 (35) [M$^+$], 228 (13), 200 (100), 186 (29), 184 (26), 172 (29), 159 (44), 158 (83), 130 (41), 102 (16), 89 (18). Anal. Calcd for $C_{15}H_{17}NO_3$ (259.30): C, 69.48; H, 6.61; N, 5.40. Found: C, 69.50; H, 6.58; N, 5.39 .

*(E)-Ethyl 2-[3-(butylimino)isobenzofuran-1(3H)-ylidene]acetate (**4a′**-E):* yield 134.2 mg, starting from 141.0 mg of *N*-butyl-2-ethynylbenzamide (70%); yellow solid; mp 57−58 °C; IR (KBr) ν = 2959 (w), 2929 (w), 1714 (m), 1640 (s), 1475 (w), 1398 (w), 1378 (w), 1249 (m), 1208 (m), 1144 (m), 1102 (m), 1051 (m), 851 (w), 781 (w), 669 (w) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 9.09−9.01 (m, 1 H), 7.92−7.85 (m, 1 H), 7.67−7.55 (m, 2 H), 5.95 (s, 1 H), 4.27 (q, *J* = 7.1, 2 H), 3.66 (t, *J* = 7.1, 2 H), 1.75−1.62 (m, 2 H), 1.51−1.37 (m, 2 H), 1.35 (t, *J* = 7.1, 3 H), 0.96 (t, *J* = 7.3, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 166.6, 161.6, 152.8, 133.8, 132.6, 132.04, 131.96, 127.7, 122.6, 97.2, 60.3, 47.9, 32.9, 20.6, 14.4, 13.9; GC−MS *m*/*z* = 273 (12) [M$^+$], 244 (11), 230 (19), 200 (89), 186 (44), 172 (100), 159 (65), 145 (20), 130 (76), 102 (21), 89 (11). Anal. Calcd for $C_{16}H_{19}NO_3$ (273.33): C, 70.31; H, 7.01; N, 5.12. Found: C, 70.33; H, 7.02; N, 5.11.

*(E)-Methyl 2-[3-(benzylimino)isobenzofuran-1(3H)-ylidene]-acetate (**4b**-E):* yield 123.4 mg, starting from 165.0 mg of *N*-benzyl-2-ethynylbenzamide (60%); yellow solid mp 53−54 °C; IR (KBr) ν =

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2927 (m), 2854 (w), 1710 (s), 1648 (s), 1470 (m), 1385 (w), 1261 (m), 1208 (m), 1146 (m), 1109 (w), 1053 (m), 979 (m), 861 (m), 775 (m), 735 (m), 705 (m), 669 (m), 626 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 9.08−9.00 (m, 1 H), 7.97−7.89 (m, 1 H), 7.67−7.54 (m, 2 H), 7.49−7.22 (m, 5 H), 5.99 (s, 1 H), 4.87 (s, 2 H), 3.80 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 166.8, 161.7, 153.6, 139.6, 133.8, 132.23, 132.16, 128.5, 127.9, 127.7, 126.9, 122.9, 97.2, 51.9, 51.5; GC−MS m/z = 293 (22) [M^+], 262 (4), 234 (19), 232 (26), 130 (6), 102 (5), 91 (100), 65 (13). Anal. Calcd for $C_{18}H_{15}NO_3$ (293.32): C, 73.71; H, 5.15; N, 4.78. Found: C, 73.70; H, 5.12; N, 4.80.

(E)-Methyl 2-[3-(phenylimino)isobenzofuran-1(3H)-ylidene]-acetate ***(4c-E)****:* yield 113.6 mg, starting from 155.0 mg of 2-ethynyl-*N*-phenylbenzamide (58%); yellow solid; mp 97−98 °C; IR (KBr) ν = 2939 (m), 1705 (s), 1647 (m), 1491 (w), 1379 (m), 1193 (w), 1138 (m), 847 (m), 762 (m), 692 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 9.10−9.03 (m, 1 H), 8.07−8.01 (m, 1 H), 7.73−7.62 (m, 2 H), 7.45−7.32 (m, 4 H), 7.24−7.16 (m, 1 H), 5.99 (s, 1 H), 3.80 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 166.6, 161.7, 151.8, 144.9, 133.4, 132.9, 132.6, 132.2, 128.7, 127.6, 125.2, 123.9, 123.3, 98.1, 51.5; GC−MS m/z = 279 (56) [M^+], 248 (37), 236 (8), 220 (100), 191 (8), 165 (29), 96 (5), 77 (13). Anal. Calcd for $C_{17}H_{13}NO_3$ (279.29): C, 73.11; H, 4.69; N, 5.02. Found: C, 73.10; H, 4.69; N, 5.05.

(E)-Methyl 2-[3-(tert-butylimino)isobenzofuran-1(3H)-ylidene]-acetate ***(4d-E)****:* yield 127.2 mg, starting from 141.0 mg of *N*-*tert*-butyl-2-ethynylbenzamide (70%); yellow solid; mp 68−69; IR (KBr) ν = 2967 (m), 2870 (w), 1711 (s), 1644 (s), 1474 (m), 1364 (w), 1261 (m), 1206 (m), 1146 (s), 1046 (s), 976 (m), 860 (w), 778 (m), 678 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 9.08−8.97 (m, 1 H), 7.91−7.81 (m, 1 H), 7.67−7.53 (m, 2 H), 5.94 (s, 1 H), 3.80 (s, 3 H), 1.44 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 167.0, 162.1, 149.4, 133.9, 132.9, 132.0, 131.8, 127.5, 123.0, 96.3, 55.1, 51.4, 30.5; GC−MS m/z = 259 (9) [M^+], 244 (35), 203 (23), 172 (100), 145 (37), 130 (35), 106 (11), 101 (10), 57 (35). Anal. Calcd for $C_{15}H_{17}NO_3$ (259.30): C, 69.48; H, 6.61; N, 5.40. Found: C, 69.45; H, 6.60; N, 5.43 .

Methyl 2-[3-(phenylimino)isobenzofuran-1(3H)-ylidene]-hexanoate ***(4f)****:* yield 188.2 mg, starting from 194.0 mg of 2-(hex-1-ynyl)-*N*-phenylbenzamide (80%) (mixture of diastereoisomers *Z*/*E*, *Z*/*E* ratio ca. 1.4, determined by ^1H NMR); yellow oil; IR (film) ν = 2955 (m), 2926 (s), 2857 (m), 1715 (s), 1660 (s), 1624 (m), 1593 (m), 1530 (w), 1489 (m), 1455 (m), 1347 (w), 1314 (w), 1262 (m), 1212 (s), 1119 (w), 1064 (m), 1041 (m), 762 (m), cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 8.56−8.48 [*Z* (m, 1 H)], 8.38 [*E* (d, *J* = 7.9, 1 H)], 8.07−8.01 [*Z* (m, 1 H)], 7.64−7.48 [*Z* (m, 2 H) + *E* (m, 2 H)], 7.43−7.30 [*Z* (m, 4 H), + *E* (m, 4 H)], 7.21−7.08 [*Z* (m, 1 H) + *E* (m, 2 H)], 3.92 [*E* (s, 3 H)], 3.88 [*Z* (s, 3 H)], 2.60 [*Z* (t, *J* = 7.9, 2 H)], 2.51 [*E* (t, *J* = 7.3, 2 H)], 1.60−1.46 [*Z* (m, 2 H) + *E* (m, 2 H)], 1.45−1.24 [*Z* (m, 2 H) + *E* (m, 2 H)], 0.90 [*Z* (t, *J* = 7.3, 3 H)], 0.85 [*E* (t, *J* = 7.3, 3 H)]; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 168.1, 166.8, 159.4, 155.5, 152.4, 148.6, 146.1, 145.2, 134.0, 132.5, 132.4, 131.0, 130.9, 128.71, 128.65, 128.1, 127.6, 126.2, 125.1, 124.2, 123.8, 123.7, 123.4, 122.5, 113.6, 109.1, 52.2, 52.0, 31.8, 31.4, 29.3, 28.8, 22.7, 22.1, 13.8, 13.7; GC−MS m/z = 335 (100) [M^+], 320 (5), 304 (9), 293 (12), 278 (31), 261 (12), 233 (20), 208 (28), 190 (11), 165 (6), 114 (4), 77 (19). Anal. Calcd for $C_{21}H_{21}NO_3$ (335.40): C, 75.20; H, 6.31; N, 4.18. Found: C, 75.19; H, 6.33; N, 4.20 .

Ethyl 2-[3-(phenylimino)isobenzofuran-1(3H)-ylidene]hexanoate ***(4f′)****:* yield 203.2 mg, starting from 194.0 mg of 2-(hex-1-ynyl)-*N*-phenylbenzamide (83%) (mixture of diastereoisomers *Z*/*E*, *Z*/*E* ratio ca. 1.0, determined by ^1H NMR); yellow oil. IR (film) ν = 2958 (m), 2925 (m), 1710 (s), 1664 (s), 1592 (s), 1489 (w), 1313 (w), 1262 (w), 1210 (m), 1064 (s), 764 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 8.57−8.50 [*Z* (m, 1 H)], 8.37 [*E* (d, *J* = 8.0, 1 H)], 8.06−8.00 [*Z* (m, 1 H)], 7.65−7.50 [*Z* (m, 2 H) + *E* (m, 2 H)], 7.47−7.30 [*Z* (m, 4 H), + *E* (m, 4 H)], 7.23−7.16 [*Z* (m, 1 H) + *E* (m, 2 H)], 4.40 [*Z* or *E* (q, *J* = 7.1, 2 H)], 4.35 [*E* or *Z* (q, *J* = 7.1, 2 H)], 2.66−2.56 [*Z* or *E* (m, 2 H)], 2.51 [*E* or *Z* (d, *J* = 7.3, 2 H)], 1.62−1.47 [*Z* (m, 2 H) + *E* (m, 2 H)], 1.45−1.22 [*Z* (m, 5 H) + *E* (m, 5 H)] 0.90 [*Z* or *E* (t, *J* = 7.3, 3 H)], 0.88 [*E* or *Z* (t, *J* = 7.3, 3 H)]; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 167.7, 166.4, 159.0, 155.2, 152.4, 148.5, 146.3, 145.3, 134.1, 132.45, 132.35, 130.8, 128.7, 128.6, 128.0, 127.5, 126.1, 125.1, 124.2, 123.7, 123.6, 123.4, 122.5, 113.9, 109.3, 61.4, 60.9, 31.8, 31.3, 29.4, 28.7, 22.6, 22.1, 14.3, 13.8, 13.7; GC−MS m/z = 349 (100) [M^+], 320 (9), 292 (18), 264 (25), 248 (10), 234 (23), 220 (13), 208 (16), 190 (12), 165 (15), 89 (13), 77 (30). Anal. Calcd for $C_{22}H_{23}NO_3$ (349.42): C, 75.62; H, 6.63; N, 4.01. Found: C, 75.64; H, 6.66; N, 3.99 .

Methyl 2-[3-(butylimino)isobenzofuran-1(3H)-ylidene]hexanoate ***(4g)****:* yield 165.9 mg, starting from 180.0 mg of *N*-butyl-2-(hex-1-ynyl)benzamide (75%) (mixture of diastereoisomers *E*/*Z*, *E*/*Z* ratio ca. 6.2, determined by ^1H NMR); colorless solid; mp 57−58 °C; IR (KBr) ν = 2956 (m), 2929 (m), 2863 (m), 1723 (s), 1671 (s), 1629 (m), 1456 (m), 1429 (m), 1348 (m), 1312 (m), 1261 (w), 1207 (m), 1105 (m), 1059 (s), 768 (m), 667 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 8.51−8.45 [*Z* (m, 1 H)], 8.19−8.13 [*E* (m, 1 H)], 7.90−7.84 [*Z* (m, 1 H)], 7.60−7.26 [*E* (m, 3 H), + *Z* (m, 2 H)], 3.92 [*E* (s, 3 H)], 3.87 [*Z* (s, 3 H)], 3.71−3.62 [*Z* (t, *J* = 7.3, 2 H)], 3.50 [*E* (t, *J* = 7.1, 2 H)], 2.71−2.61 [*Z* (m, 2 H)], 2.60 [*E* (t, *J* = 7.5, 2 H)], 1.77−1.33 [*E* (m, 8 H) + *Z* (m, 8 H)], 1.01−0.91 [*E* (m, 6 H) + *Z* (m, 6 H)]; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 167.2, 159.6, 148.5, 132.2, 131.7, 131.5, 130.7, 130.2, 129.6, 128.9, 127.7, 126.7, 126.1, 125.0, 123.5, 123.3, 122.7, 111.9, 108.3, 52.0, 46.0, 32.9, 32.2, 29.5, 22.3, 20.8, 14.0, 13.9, 13.8; GC−MS m/z = 315 (19) [M^+], 286 (33), 284 (19), 272 (84), 259 (80), 226 (100), 217 (31), 214 (24), 198 (33), 185 (72), 184 (66), 170 (50), 158 (14), 143 (24), 130 (83), 115 (26), 102 (20), 85 (11). Anal. Calcd for $C_{19}H_{25}NO_3$ (315.41): C, 72.35; H, 7.99; N, 4.44. Found: C, 72.33; H, 8.00; N, 4.45 .

Methyl 2-[3-(benzylimino)isobenzofuran-1(3H)-ylidene]-hexanoate ***(4h)****:* yield 110.2 mg, starting from 204.0 mg of *N*-benzyl-2-(hex-1-ynyl)benzamide (45%) (mixture of diastereoisomers *E*/*Z*, *E*/*Z* ratio ca. 4.9, determined by ^1H NMR) yellow oil; IR (film) ν = 2956 (s), 2931 (m), 2871 (m), 1723 (s), 1666 (s), 1486 (m), 1435 (m), 1345 (m), 1309 (m), 1259 (m), 1206 (m), 1106 (m), 1049 (m), 734 (m), 698 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 8.46 [*Z* (d, *J* = 7.8, 1 H)], 8.30 [*E* (d, *J* = 7.7, 1 H)], 7.91 [*Z* (d, *J* = 7.3, 1 H)], 7.61−7.20 [*E* (m, 8 H), + *Z* (m, 7 H)], 4.87 [*Z* (s, 2 H)], 4.73 [*E* (s, 2 H)], 3.92 [*E* (s, 3 H)], 3.88 [*Z* (s, 3 H)], 2.69 [*Z* (t, *J* = 7.6, 2 H)], 2.61 [*E* (t, *J* = 7.6, 2 H)], 1.73−1.31 [*E* (m, 4 H) + *Z* (m, 4 H)], 1.00−0.87 [*E* (m, 3 H) + *Z* (m, 3 H)]; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 167.1, 159.4, 149.5, 140.7, 134.7, 134.4, 131.94, 131.86, 130.7, 130.2, 129.6, 128.5, 128.3, 127.9, 127.6, 126.9, 126.8, 126.5, 126.0, 125.0, 123.6, 122.9, 112.5, 108.7, 102.8, 52.1, 51.9, 50.8, 50.0, 32.2, 31.2, 29.5, 28.5, 22.6, 22.3, 13.9, 13.8; GC−MS *Z*: m/z = 349 (6) [M^+] 318 (3), 293 (27), 261 (52), 232 (6), 130 (7), 91 (100); *E*: m/z = 349 (5), 318 (4), 293 (32), 261 (55), 207 (11), 193 (5), 130 (9), 117 (11), 91 (100). Anal. Calcd for $C_{22}H_{23}NO_3$ (349.42): C, 75.62; H, 6.63; N, 4.01. Found: C, 75.61; H, 6.65; N, 4.02.

(E)-Methyl 2-phenyl-2-[3-(phenylimino)isobenzofuran-1(3H)-ylidene]acetate ***(4i-E)****:* yield 136.8 mg, starting from 208.0 mg of *N*-phenyl-2-(2-phenylethynyl)benzamide (55%); yellow solid; mp 56−57 °C; IR (KBr) ν = 3019 (w), 1712 (s), 1691(s), 1613 (m), 1590 (m), 1489 (w), 1300 (w), 1268 (w), 1216 (m), 1053 (s), 1006 (m), 757 (s), 692 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 8.29 (d, *J* = 7.1, 1 H), 8.07−8.02 (m, 1 H), 7.68−7.57 (m, 2 H), 7.50−7.43 (m, 2 H), 7.43−7.28 (m, 5 H), 7.26−7.19 (m, 2 H), 7.15−7.07 (m, 1 H), 3.89 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 167.8, 153.3, 151.8, 144.5, 134.1, 134.0, 132.4, 132.2, 131.2, 129.5, 128.6, 128.2, 127.9, 125.5, 125.2, 124.9, 123.7, 112.7, 52.5; GC−MS m/z = 355 (36) [M^+], 324 (16), 296 (100), 295 (46), 267 (21), 246 (5), 219 (5), 190 (7), 165 (7), 77 (16). Anal. Calcd for $C_{23}H_{17}NO_3$ (355.39): C, 77.73; H, 4.82; N, 3.94. Found: C, 77.71; H, 4.85; N, 3.90.

(E)-Methyl 2-cyclohexenyl-2-[3-(phenylimino)isobenzofuran-1(3H)-ylidene]acetate ***(4j-E)****:* yield 196.4 mg, starting from 211.0 mg of 2-(2-cyclohexenylethynyl)-*N*-phenylbenzamide (78%); yellow solid; mp 189−190 °C; IR (KBr) ν = 2930 (s), 2958 (w), 1724 (s), 1660 (s), 1592 (m), 1489 (m), 1434 (m), 1347 (m), 1312 (m), 1221 (m), 1090 (m), 1057 (m), 771 (m), 694 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 8.42−8.33 (m, 1 H), 7.60−7.51 (m, 1 H), 7.48−7.29 (m, 4 H), 7.21−7.06 (m, 3 H), 6.10 (s, br, 1 H), 3.84 (s, 3 H), 2.19−2.03 (m, 4 H), 1.72−1.53 (m, 4 H); ^{13}C NMR (75 MHz,

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$CDCl_3$) δ = 167.6, 156.2, 148.4, 146.2, 132.5, 131.8, 131.3, 128.6, 128.3, 127.6, 124.6, 123.7, 123.4, 122.7, 108.3, 52.3, 25.63, 25.59, 22.2, 21.5; GC−MS m/z = 359 (100) [M^+], 344 (10), 316 (14), 300 (10), 272 (8), 208 (7), 190 (10), 179 (9), 165 (8), 114 (3), 77 (24). Anal. Calcd for $C_{23}H_{21}NO_3$ (359.42): C, 76.86; H, 5.89; N, 3.90. Found: C, 76.86; H, 5.91; N, 3.92.

*(E)-Methyl 2-[3-(butylimino)isobenzofuran-1(3H)-ylidene]-2-cyclohexenylacetate (**4k-E**):* yield 161.8 mg, starting from 197.0 mg of *N*-butyl-2-(2-cyclohexenylethynyl)benzamide (68%); colorless oil; IR (film) ν = 2933 (m), 2863 (w), 1723 (s), 1668 (s), 1435 (w), 1338 (m), 1307 (w), 1220 (m), 1089 (m), 1051 (w), 756 (s) (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 8.15 (d, J = 8.4, 1 H), 7.50−7.24 (m, 3 H), 6.21−6.13 (m, 1 H), 3.82 (s, 3 H), 3.52−3.43 (m, 2 H), 2.38−2.28 (m, 2 H), 2.23−2.12 (m, 2 H), 1.79−1.60 (m, 6 H), 1.53−1.38 (m, 2 H), 0.96 (t, J = 7.3, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 167.8, 156.5, 148.3, 132.4, 131.7, 131.5, 127.8, 126.6, 125.0, 123.1, 122.6, 107.7, 52.0, 45.9, 32.8, 25.7, 25.6, 22.3, 21.6, 20.7, 13.9; GC−MS m/z = 339 (17) [M^+], 322 (25), 310 (25), 296 (89), 280 (100), 264 (18), 258 (31), 226 (66), 170 (29), 142 (9) 114 (14), 109 (78), 81 (39). Anal. Calcd for $C_{21}H_{25}NO_3$ (339.43): C, 74.31; H, 7.42; N, 4.13. Found: C, 74.30; H, 7.41; N, 4.11.

Formation of a Mixture of Methyl 2-[3-(Phenylimino)-isobenzofuran-1(3*H*)-ylidene]hexanoate 4f and Methyl 3-Butyl-1-oxo-1*H*-isochromene-4-carboxylate 5f by PdI_2-Catalyzed Heterocyclization−Alkoxycarbonylation of 2-(Hex-1-ynyl)-*N*-phenylbenzamide 1f (eq 2). A 250 mL stainless steel autoclave was charged in the presence of air with PdI_2 (3.6 mg, 1.0×10^{-2} mmol), KI (16.8 mg, 0.1 mmol), and a solution of **1f** (140 mg, 0.5 mmol) in MeOH (25 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 5 h, the autoclave was cooled, degassed, and opened. The solvent was evaporated, and the products were separated by column chromatography on neutral alumina (eluent: hexane−AcOEt from 99:1 to 95:5) to give methyl 3-butyl-1-oxo-1*H*-isochromene-4-carboxylate **5f** and methyl 2-[3-(phenylimino)isobenzofuran-1(3*H*)-ylidene]hexanoate **4f** (*Z*/*E* ca. 1.4, by ^1H NMR) in that order.

*Methyl 3-Butyl-1-oxo-1H-isochromene-4-carboxylate (**5f**):* pale yellow oil; IR (film) ν = 2958 (m), 2938 (m), 1728 (vs), 1631 (m), 1488 (w), 1457 (m), 1355 (m), 1319 (m), 1258 (m), 1215 (m), 1058 (m), 1024 (w), 758 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 8.29 (d, J = 7.9, 1 H), 7.79−7.63 (m, 2 H), 7.56−7.45 (m, 1 H), 3.97 (s, 3 H), 2.69 (t, J = 7.6, 2 H), 1.83−1.63 (m, 2 H), 1.50−1.32 (m, 2 H), 0.95 (t, J = 6.7, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 166.4, 161.3, 161.0, 135.0, 134.7, 129.7, 128.2, 124.2, 119.6, 110.0, 52.4, 32.5, 29.8, 22.4, 13.7; GC−MS m/z = 260 (99) [M^+], 229 (48), 218 (9), 203 (100), 199 (36), 190 (37), 186 (78), 176 (71), 161 (7), 148 (53), 133 (33), 115 (10), 104 (26), 88 (28), 57 (39). Anal. Calcd for $C_{15}H_{16}O_4$ (260.29): C, 69.22; H, 6.20. Found: C, 69.23; H, 6.23.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Table S1, Figures S1−S4, summary of X-ray data for compounds **3da**-*E*, **3ea**-*Z*, **4d**-*E*, and **4i**-*E* (Tables S2−S13 and Figures S5−S8), X-ray crystallographic files (CIF) for compounds **3da**-*E*, **3ea**-*Z*, **4d**-*E*, and **4i**-*E* (CCDC 975358−975361), and copies of ^1H and ^{13}C NMR spectra for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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