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A Zinc-Mediated Deprotective Annulation Approach to New Polycyclic Heterocycles

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Abstract: A straightforward approach to new polycyclic heterocycles, 1*H*-benzo[4,5]imidazo[1,2-*c*][1,3]oxazin-1-ones, is presented. It is based on the $ZnCl_2$-promoted deprotective 6-*endo-dig* heterocyclization of *N*-Boc-2-alkynylbenzimidazoles under mild conditions (CH_2Cl_2, 40 °C for 3 h). The zinc center plays a dual role, as it promotes Boc deprotection (with formation of the *tert*-butyl carbocation, which can be trapped by substrates bearing a nucleophilic group) and activates the triple bond toward intramolecular nucleophilic attack by the carbamate group. The structure of representative products has been confirmed by X-ray diffraction analysis.

Keywords: alkynes; annulation; benzimidazoxazinones; heterocycles; polycyclic heterocycles; heterocyclization; zinc

1. Introduction

The development of efficient methods for the synthesis of high value added polycyclic heterocyclic derivatives by metal-promoted annulation of acyclic precursors is one of the most important area of research in heterocyclic chemistry [1–5]. Polycyclic heterocyclic systems, in fact, are largely present as fundamental cores in natural products and in biologically active compounds [6–11], and the possibility to obtain them by a simple cyclization process starting from readily available substrates is particularly attractive [1–5].

Among acyclic substrates able to undergo a metal-promoted cyclization to give a polycyclic heterocycle, functionalized alkynes bearing a suitably placed heteronucleophile play a major role, as the triple bond can be easily electrophilically activated by a suitable metal species thus promoting the cyclization by intramolecular nucleophilic attack [1–5]. Usually, processes like these are promoted by costly metals (mainly gold [12–19], palladium [20–23], rhodium [24–26], platinum [27–29], and, occasionally, ruthenium [30]), while the use of less expensive metal species, such as cobalt [31], nickel [32], copper [33–36], zinc [37–40], and silver [41,42] compounds, has been scantly reported in the literature, and applied to a limited number of examples.

In this work, we report on the use of very simple and inexpensive $ZnCl_2$ as a promoter for the efficient deprotective heterocyclization of *N*-Boc-2-alkynylbenzimidazoles **1**, to give access to novel polycyclic heterocycles, that are, 1*H*-benzo[4,5]imidazo[1,2-*c*][1,3]oxazin-1-ones **2** (Scheme 1). It is worth mentioning in this context that the cyclization of *O*-Boc propargyl alcohols to give 4*H*-1,3-dioxin-2-ones and/or 4-alkylidene-1,3-dioxolan-2-ones

has been previously reported to occur with mercuric triflate as the catalyst [43]. It is also important to note that some excellent reviews on Zn-catalyzed reactions have appeared in the recent literature [44–48].
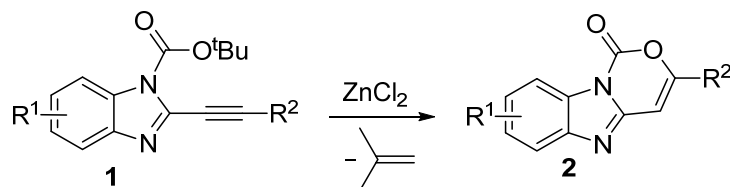
Scheme 1. This work*:* ZnCl$_2$-assisted heterocyclization of *N*-Boc-alkynylbenzimidazoles **1** to benzimidazoxaxinones **2**.

## 2. Results and Discussion

It is well known that zinc (II) compounds are able to promote Boc deprotection [49–54]. In particular, an excess of ZnBr$_2$ has been successfully employed for the deprotection of *N*-Boc secondary amines [52] as well as of *tert*-butyl esters [53,54]. Considering the importance of developing new approaches to the synthesis of polycyclic heterocycles by heterocyclization processes promoted by non-noble and inexpensive metal species, we have explored the possibility to access new polycyclic heterocycles, that are 1*H*-benzo[4,5]imidazo[1,2-*c*][1,3]oxazin-1-ones **2**, starting from readily available *N*-Boc-2-alkynylbenzimidazoles **1**, by Zn(II)-assisted deprotective heterocyclization (Scheme 1). According to our rationale, the zinc center should play a double role, that is, to promote deprotection to give a carbamate species **A** (with elimination of isobutene and H$^+$ from the ensuing *tert*-butyl carbocation [52–54]) and then assist a 6-*endo-dig* heterocyclization by intramolecular nucleophilic attack of the free carbamate group of species **B** (in equilibrium with **A**) on the triple bond activated by coordination to Zn^{2+} (with the zinc center stabilized by chelation by the benzimidazole nitrogen). This would lead to organizinc intermediate **C**, whose protonolysis would then afford the polycyclic heterocycles **2** (Scheme 2; zinc counteranions have been omitted for clarity).
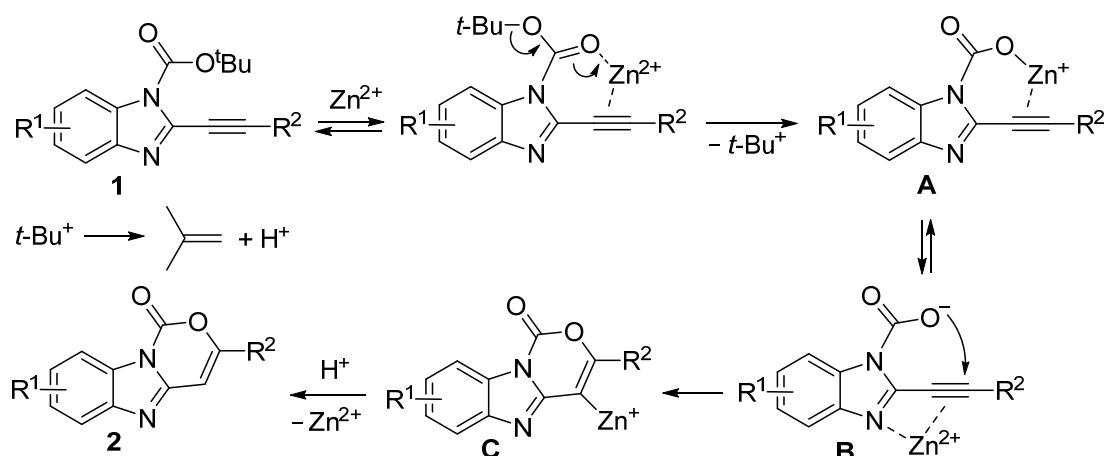
Scheme 2. Mechanistic hypothesis for the formation of polycyclic heterocycles **2** by Zn^{2+}-mediated sequential deprotection - 6-*endo-dig* heterocyclization of *N*-Boc-alkynylbenzimidazoles **1**.

The first experiments were performed using *N*-Boc-2-(hex-1-in-1-yl)-1*H*-benzo[*d*]imidazole **1a** as substrate (R^1 = H, R^2 = Bu) (prepared by alkynylation of *N*-Boc-2-bromo-1*H*-benzo[*d*]imidazole, see the Supplementary Materials for details), which was allowed to react in CH$_2$Cl$_2$ as the solvent at room temperature in the presence of ZnBr$_2$ (1 equiv). Under these conditions, after 3 h reaction time, substrate conversion was 51%, while the desired 3-butyl-1*H*-benzo[4,5]imidazo[1,2-*c*][1,3]oxazin-1-one **2a** was isolated in 25% yield. The structure of **2a** was unequivocally confirmed by XRD analysis (see the

Supplementary Materials for XRD data). The X-ray structure of **2a**, shown in Figure 1, confirmed that the heterocyclization process at intermediate **B** level occurred in a 6-*endo-dig* fashion (with closure to a 6-membered ring) rather than in the possible alternative 5-*exo-dig* fashion (with closure to a five-membered ring).
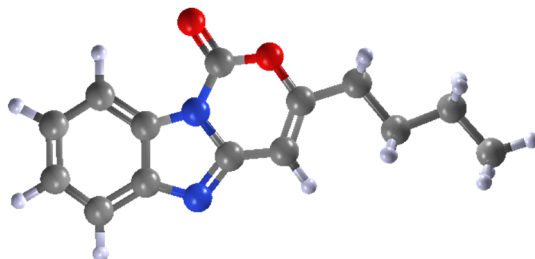
Figure 1. Molecular structure of 3-butyl-1*H*-benzo[4,5]imidazo[1,2-*c*][1,3]oxazin-1-one **2a**. Color legend: carbon (light grey), hydrogen (white), oxygen (red), nitrogen (blue) (CCDC 2050576).
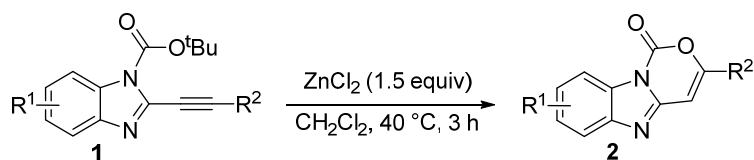
In spite of the low yield, this initial result was encouraging, since it confirmed the validity of our work hypothesis and the possibility to synthesize novel polycyclic heterocycles with a very simple approach and using an inexpensive promoter. In order to improve the reaction performance, and achieve a higher **2a** yield, we then changed some operative parameters (Table 1, entries 2–9). Practically no reaction occurred by changing the solvent to MeOH (Table 1, entry 2), while only traces of **2a** were detected in acetone (Table 1, entry 3). Lowering the amount of $ZnBr_2$ significantly suppressed the reaction (Table 1, entry 4). On the other hand, the use of 1.5 or 2 equiv of $ZnBr_2$ was beneficial, **2a** being formed in ca. 70% isolated yield (Table 1, entries 5 and 6, respectively). Better results with respect to the parent reaction (Table 1, entry 1) were also obtained by increasing the **1a** concentration from 0.5 (Table 1, entry 1) to 1 mmol/mL of CH_2Cl_2 (Table 1, entry 7), while more diluted conditions led to a lower **2a** yield (Table 1, entry 8). Predictably, a faster reaction was observed at 40 °C rather than 25 °C, with a higher yield of **2a** (Table 1, entry 9) with respect to the initial experiment (Table 1, entry 1). Under the optimized conditions (40 °C in CH_2Cl_2 in the presence of 1.5 equiv of $ZnBr_2$, with a substrate concentration of 1 mmol per mL of solvent), **2a** could be finally obtained in a yield as high as 79% (Table 1, entry 10).

Very interestingly, the reaction was also successful using $ZnCl_2$ (Table 1, entry 11) or ZnI_2 (Table 1, entry 12), the best results in terms of **2a** yield being obtained with $ZnCl_2$ (82%, Table 1, entry 11). This result, associated with the lower cost of $ZnCl_2$, made $ZnCl_2$ the promoter of choice for realizing the transformation of **1a** into benzimidazoxazinone **2a** and for the subsequent extension to other differently substituted substrates (Table 2). Thus, to assess the generality of the reaction, various *N*-Boc-alkynylbenzimidazoles **1** (bearing different R^1 and R^2 groups; prepared as detailed in the Supplementary Materials) were subjected to the optimized reaction conditions with $ZnCl_2$ as the promoter (Table 2, entries 2–15).

Table 1. ZnX$_2$-promoted deprotective heterocyclization of *N*-Boc-2-(hex-1-in-1-yl)-1*H*-benzo[*d*]imidazole **1a** under different conditions [a].
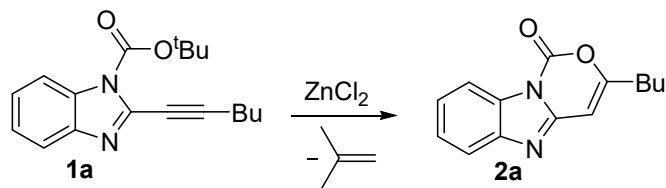
Entry	ZnX$_2$ (Equiv)	T (°C)	Solvent	Concentration of 1a [b]	Conversion of 1a (%) [c]	Yield of 2a (%) [d]
1	ZnBr$_2$ (1)	25	CH$_2$Cl$_2$	0.5	51	25
2	ZnBr$_2$ (1)	25	MeOH	0.5	3	0
3	ZnBr$_2$ (1)	25	acetone	0.5	12	Traces
4	ZnBr$_2$ (0.5)	25	CH$_2$Cl$_2$	0.5	9	6
5	ZnBr$_2$ (1.5)	25	CH$_2$Cl$_2$	0.5	100	72
6	ZnBr$_2$ (2)	25	CH$_2$Cl$_2$	0.5	100	70
7	ZnBr$_2$ (1)	25	CH$_2$Cl$_2$	1.0	62	33
8	ZnBr$_2$ (1)	25	CH$_2$Cl$_2$	0.2	42	10
9	ZnBr$_2$ (1)	40	CH$_2$Cl$_2$	0.5	100	63
10	ZnBr$_2$ (1.5)	40	CH$_2$Cl$_2$	1.0	100	79
11	ZnCl$_2$ (1.5)	40	CH$_2$Cl$_2$	1.0	100	82
12	ZnI$_2$ (1.5)	40	CH$_2$Cl$_2$	1.0	100	77

[a] All reactions were carried out for 3 h. [b] Mmol of starting **1a** per mL of solvent. [c] Based on unreacted **1a**, upon isolation from the reaction mixture. [d] Isolated yield based on starting **1a**.

Table 2. Synthesis of 1*H*-benzo[4,5]imidazo[1,2-*c*][1,3]oxazin-1-ones **2** by ZnCl$_2$-promoted deprotective heterocyclization of *N*-Boc-2-alkynylbenzimidazoles **1** [a].

Entry	1	2	Yield of 2 (%) [b]
1	**1a**	**2a**	82
2	**1b**	**2b**	77
3	**1c**	**2c**	76
4	**1d**	**2d**	83
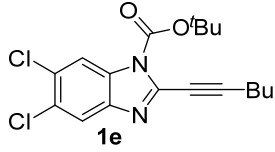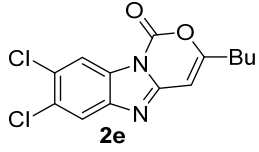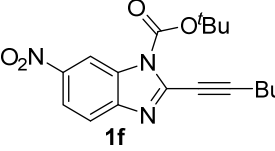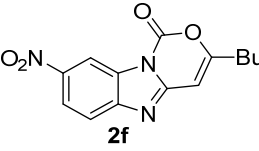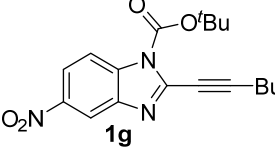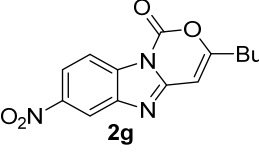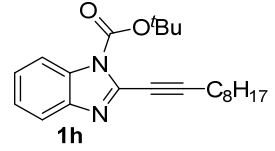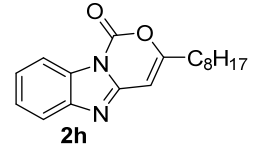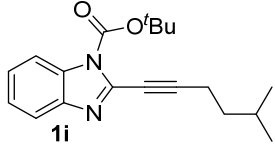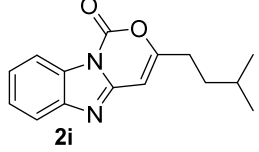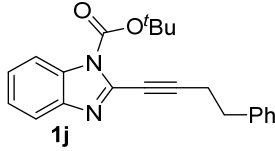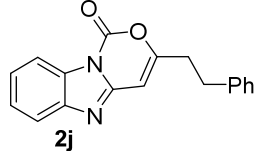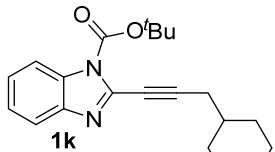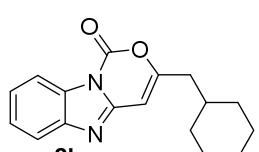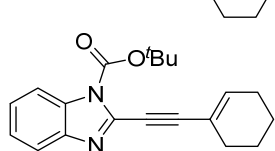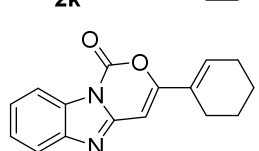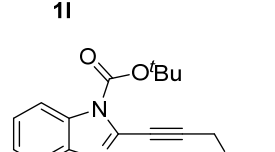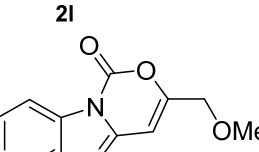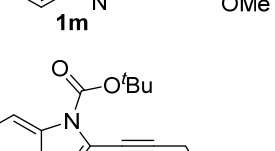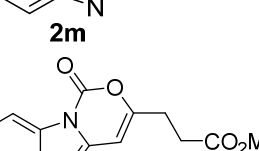
Table 2. *Cont.*

Entry	1	2	Yield of 2 (%) [b]
5	**1e**	**2e**	77
6	**1f**	**2f**	45 [c]
7	**1g**	**2g**	30 [d]
8	**1h**	**2h**	85
9	**1i**	**2i**	82
10	**1j**	**2j**	80
11	**1k**	**2k**	70
12	**1l**	**2l**	66
13	**1m**	**2m**	60
14	**1n**	**2n**	74

Table 2. *Cont.*

Entry	1	2	Yield of 2 (%) [b]
15	**1o**	**2o'**	66

[a] All reactions were carried out in CH$_2$Cl$_2$ (1 mmol of **1** per mL of solvent) at 40 °C for 3 h. [b] Isolated yield based on starting **1**. [c] The reaction led also to 2-(hex-1-yn-1-yl)-6-nitro-1*H*-benzo[*d*]imidazole **3f** in 20% isolated yield. [d] The reaction led also to 2-(hex-1-yn-1-yl)-5-nitro-1*H*-benzo[*d*]imidazole **3g** in 31% isolated yield.

As can be seen from Table 2, entries 2–5, excellent results were obtained with substrates still with R^2 = Bu and bearing either electron-donating (methyl or methoxy; yields of the corresponding products **2b–d** were 76–83%, Table 2, entries 2–4) or electron-withdrawing chlorine substituents (yield of **2e** = 77%, Table 2, entry 5) on the aromatic ring. On the other hand, inferior results were observed with substrates **1f** and **1g**, bearing a strong electron-withdrawing nitro substituent (yields of **2f** and **2g** were 45% and 30%, Table 2, entries 6 and 7, respectively). With these substrates, complete Boc removal competed with heterocyclization, as confirmed by the formation of not negligible amounts of deprotected compounds **3f** and **3g** (20% and 31%, respectively, Table 2, entries 6 and 7) (Scheme 3), not observed in other cases. Clearly, the formation of these byproducts from substrates **1f** and **1g** is due to the diminished nucleophilicity of the carbamate intermediate **B** (Scheme 2) caused by the strong electron-withdrawing effect of the nitro group, which makes decarboxylation to compete with cyclization. The structures of products **2c** and **2f** were confirmed by XRD analysis (see the Supplementary Materials for XRD data). The X-ray structures of **2c** and **2f**, shown in Figures 2 and 3, respectively, allowed to unequivocally establish the positions of the methoxy and nitro substituents in regioisomeric substrates **1c/1d** and **1f/1g**, respectively (as **2c** must be formed from **1c** and **2f** from **1f**).
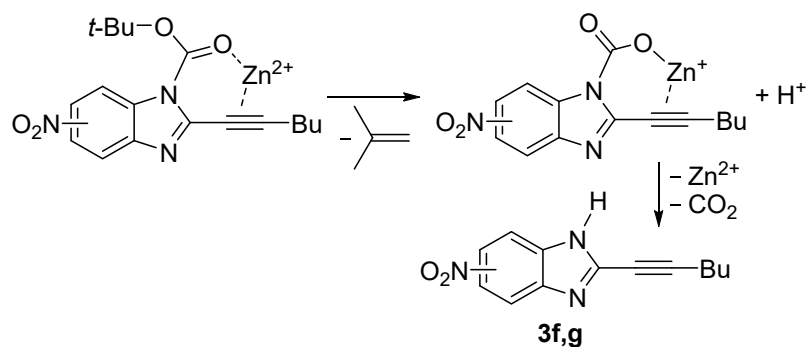
Scheme 3. Formation of byproducts **3f** and **3g** (Table 2, entries 6 and 7) by Boc deprotection of nitro-substituted substrates **1f** and **1g**, competitive with heterocyclization.
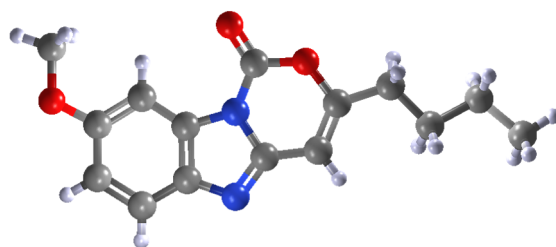
Figure 2. Molecular structure of 3-butyl-8-methoxy-1*H*-benzo[4,5]imidazo[1,2-*c*][1,3]oxazin-1-one **2c**. Color legend: carbon (light grey), hydrogen (white), oxygen (red), nitrogen (blue) (CCDC 2051334).
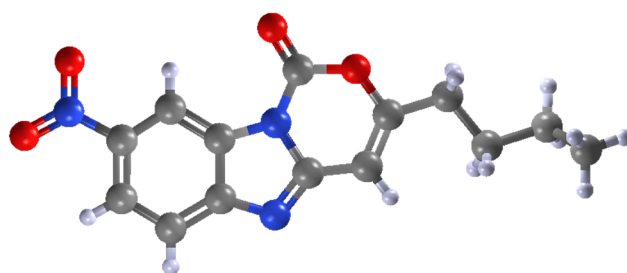
Figure 3. Molecular structure of 3-butyl-8-nitro-1*H*-benzo[4,5]imidazo[1,2-*c*][1,3]oxazin-1-one **2f**. Color legend: carbon (light grey), hydrogen (white), oxygen (red), nitrogen (blue) (CCDC 2050711).

High yields of the corresponding benzimidazoxazinones were obtained by changing the alkyl substituent on the triple bond R^2 to octyl (yield of **2h**, 85%; Table 2, entry 8), isopentyl (yield of **2i**, 82%; Table 2, entry 9), or phenethyl (yield of **2j**, 80%; Table 2, entry 10), while a slightly lower yield was observed with R^2 = cyclohexylmethyl (yield of **2k**, 70%; Table 2, entry 11). The use of a substrate with the triple bond conjugated with an alkenyl group, as in *N*-Boc-2-(cyclohex-1-en-1-ylethynyl)-1*H*-benzo[*d*]imidazole **1l**, led to a satisfactory yield of the corresponding polycyclic heterocycle **2l** (66%; Table 2, entry 12).

The method also worked nicely with substrates bearing a functionalized alkyl chain of the triple bond, as shown by the results obtained with a methoxymethyl (yield of **2m**, 60%; Table 2, entry 13) or a 2-(methoxycarbonyl) ethyl (yield of **2n**, 74%; Table 2, entry 14) group. Interestingly in the case of *N*-Boc-4-(1*H*-benzo[*d*]imidazol-2-yl) but-3-yn-1-ol **1o**, bearing a 2-hydroxyethyl group on the triple bond, the *tert*-butyl group was incorporated into the final product to give 3-(2-(*tert*-butoxy)ethyl)-1*H*-benzo[4,5]imidazo[1,2-*c*][1,3]oxazin-1-one **2o'** (66% yield; Table 1, entry 15). This is clearly due to the trapping of the *tert*-butyl carbocation, ensuing from deprotection, by the nucleophilic hydroxyl group, as shown in Scheme 4.
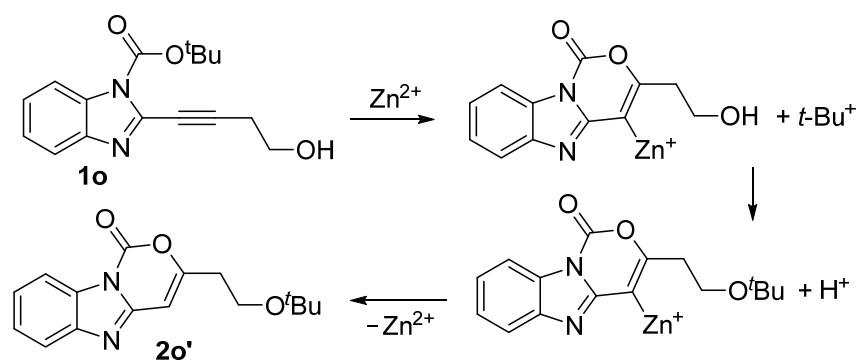
Scheme 4. Plausible mechanism for the formation of product **2o'** (chloride anions are omitted for clarity).

3. Materials and Methods

3.1. General Experimental Methods

Melting points were measured with a Leitz Laborlux 12 POL polarizing optical microscope (Leitz Italia GmbH/Srl, Lana(BZ), Italy) and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded at 25 °C in CDCl$_3$ or DMSO-d_6 at 300 MHz or 500 MHz and 75 or 125 MHz, respectively, with Me$_4$Si as internal standard, using Bruker DPX Avance 300 and Bruker DPX Avance 500 NMR spectrometers (Brucker Italia s.r.l., Milano, Italy); chemical shifts (δ) and coupling constants (*J*) are given in ppm and in Hz, respectively. IR spectra were taken with a JASCO FT-IR 4200 spectrometer (Jasco Europe s.r.l., Cremella, Lecco, Italy). All reactions were analyzed by TLC on silica gel 60 F$_{254}$ and by GC-MS using a Shimadzu QP-2010 GC–MS apparatus (Smimadzu Italia s.r.l., Milano, Italy) at 70 eV ionization voltage equipped with a 95% methyl polysiloxane–5% phenyl polysiloxane capillary column (30 m × 0.25 mm, 0.25 μm). Column chromatography was performed on silica

gel 60 (Merck, 70–230 mesh; Merck Life Science s.r.l., Milano, Italy). Evaporation refers to the removal of solvent under reduced pressure. The HRMS spectra were taken on an Agilent 1260 Infinity UHD accurate-mass Q-TOF mass spectrometer (Agilent Technologies Italia s.p.a. Cernusco sul Naviglio, Milano, Italy), equipped with an electrospray ion source (ESI) operated in dual ion mode. Ten microliters of the sample solutions (CH_3OH) were introduced by continuous infusion at a flow rate of 200 L min^{-1} with the aid of a syringe pump. Experimental conditions were performed as follows: capillary voltage, 4000 V; nebulizer pressure, 20 psi; flow rate of drying gas, 10 L/min; temperature of sheath gas, 325 °C; flow rate of sheath gas, 10 L/min; skimmer voltage, 60 V; OCT1 RF Vpp, 750 V; fragmentor voltage, 170 V. The spectra data were recorded in the *m/z* range of 100–1000 Da in a centroid pattern of full-scan MS analysis mode. The MS/MS data of the selected compounds were obtained by regulating diverse collision energy (18–45 eV).

3.2. Preparation of Substrates **1**

Substrates were prepared and characterized as described in the Supplementary Materials.

3.3. General Procedure for the Synthesis of Benzimidazoxazinone Derivatives **2**

See Table 2 for reference. A Schlenk flask was charged under nitrogen with the *N*-Boc-2-alkynylbenzimidazole **1** (1 mmol) (**1a**: 298 mg; **1b**: 326 mg; **1c**: 328 mg; **1d**: 328 mg; **1e**: 367 mg; **1f**: 343 mg; **1g**: 343 mg; **1h**: 354 mg; **1i**: 312 mg; **1j**: 346 mg; **1k**: 338 mg; **1l**: 322 mg; **1m**, 286 mg; **1n**: 328 mg; **1o**: 286 mg), anhydrous CH_2Cl_2 (1 mL), and $ZnCl_2$ (204 mg, 1.5 mmol). The reaction mixture was heated at 40 °C and then allowed to stir at this temperature for 3 h. After cooling, the reaction mixture was diluted with CH_2Cl_2 (5 mL) and water (5 mL) (for **2a-l**, **2n**, and **2o′**). Alternatively, after cooling, the solvent was evaporated, and water (20 mL) was added to the residue (for **2m**). Phases were separated the aqueous phase was washed with CH_2Cl_2 (5 mL), and the combined organic phases were dried with Na_2SO_4. After filtration and evaporation of the solvent, the product was purified by column chromatography on silica gel using hexane/AcOEt (8:2, *v/v*) as the eluent (for **2a-1l**, **2n**, and **2o′**). For the purification of **2m**, the suspension obtained as seen above was filtered, the precipitate washed with water (3 × 5 mL) and then purified by column chromatography on silica gel using hexane/AcOEt (8:2, *v/v*) as eluent. With substrates **1f** and **1g**, the reaction also led to the formation of deprotected products **3f** and **3g**, respectively (Scheme 3) (order of elution: **3f** followed by **2f**; **2g** followed by **3g**).

3.3.1. 3-Butyl-1*H*-benzo[4,5]imidazo[1,2-*c*][1,3]oxazin-1-one **2a**

Yield: 198 mg, starting from 298 mg of **1a** (82%) (Table 2, entry 1). Colorless solid, mp: 92–94 °C; IR (KBr): v = 1759 (s), 1667 (m), 1551 (w), 1450 (w), 1366 (s), 1096 (m), 972 (w), 849 (w), 748 (m) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.24–8.13 (m, 1 H, aromatic), 7.82–7.73 (m, 1 H, aromatic), 7.52–7.36 (m, 2 H, aromatic), 6.50 (s, 1 H, H-4), 2.61 (t, *J* = 7.3, 2 H, =CCH_2), 1.75 (quint, *J* = 7.3, 2 H, CH_2CH$_2$CH$_3$), 1.46 (hexuplet, *J* = 7.3, 2 H, CH_2CH$_3$), 0.98 (t, *J* = 7.3, 3 H, CH$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.9, 147.4, 144.1, 129.3, 126.3, 124.9, 119.7, 114.6, 96.6, 32.8, 28.4, 22.1, 13.7; GC/MS = 242 (M$^+$, 100), 227 (2), 213 (3), 200 (42), 185 (31), 171 (6), 158 (43); 144 (4), 130 (12); HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{14}H_{15}N_2O_2{}^+$ 243.1128; Found: 243.1132.

3.3.2. 3-Butyl-7,8-dimethyl-1*H*-benzo[4,5]imidazo[1,2-*c*][1,3]oxazin-1-one **2b**

Yield: 208 mg, starting from 326 mg of **1b** (77%) (Table 2, entry 2). Colorless solid, mp: 133–137 °C; IR (KBr): v = 1768 (s), 1667 (m), 1558 (w), 1450 (m), 1381 (s), 1111 (w), 741 (w) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.92 (s, 1 H, H-6 or H-9), 7.48 (s, 1 H, H-9 or H-6), 6.44 (s, 1 H, H-4), 2.59 (t, *J* = 7.5, 2 H, =CCH_2), 2.40 (s, 3 H, CH$_3$ at C-7 or C-8), 2.38 (s, 3 H, CH$_3$ at C-8 or C-7), 1.72 (quint, *J* = 7.5, 2 H, CH_2CH$_2$CH$_3$), 1.44 (hexuplet, *J* = 7.5, 2 H, CH_2CH$_3$), 0.98 (t, *J* = 7.5, 3 H, CH$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.0, 146.6, 144.2, 142.5, 135.3, 134.3, 127.6, 119.8, 114.7, 96.7, 32.8, 28.5, 22.1, 20.4, 13.7; GC/MS = 270 (M$^+$,

100); 255 (3), 228 (29), 213 (24), 199 (5), 186 (19), 172 (3), 158 (6), 143 (1), 130 (2), 118 (8); HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for C$_{16}$H$_{19}$N$_2$O$_2$$^+$ 271.1441; Found: 271.1446.

3.3.3. 3-Butyl-8-methoxy-1*H*-benzo[4,5]imidazo[1,2-*c*][1,3]oxazin-1-one **2c**

Yield: 207 mg, starting from 328 mg of **1c** (76%) (Table 2, entry 3). Colorless solid, mp: 96–99 °C; IR (KBr): v = 1767 (s), 1667 (m), 1489 (m), 1443 (w), 1366 (m), 1281 (m), 1204 (w), 1026 (w), 818 (m) cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ = 7.70 (d, *J* = 2.5, 1 H, H-9), 7.63 (d, *J* = 8.8, 1 H, H-6), 7.06 (dd, *J* = 8.8, 2.5, 1 H, H-7), 6.46–6.44 (m, 1 H, H-4), 2.60 (t, *J* = 7.5, 2 H, =CCH$_2$), 1.72 (quint, *J* = 7.5, 2 H, C*H*$_2$CH$_2$CH$_3$), 1.45 (hexuplet, *J* = 7.5, 2 H, C*H*$_2$CH$_3$), 0.98 (t, *J* = 7.5, 3 H, CH$_3$); ^{13}C NMR (125 MHz, CDCl$_3$): δ = 161.7, 158.0, 146.3, 144.4, 138.3, 130.2, 120.2, 115.5, 98.3, 96.8, 56.0, 32.8, 28.5, 22.1, 13.7; GC/MS: *m/z* = 272 (M$^+$, 100), 257 (17), 229 (29), 215 (22), 187 (14); HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for C$_{15}$H$_{17}$N$_2$O$_3$$^+$ 273.1234; Found: 273.1237.

3.3.4. 3-Butyl-7-methoxy-1*H*-benzo[4,5]imidazo[1,2-*c*][1,3]oxazin-1-one **2d**

Yield: 226 mg, starting from 328 mg of **1d** (83%) (Table 2, entry 4) Colorless solid, mp: 93–97 °C; IR (KBr): v = 1760 (s), 1659 (m), 1558 (w), 1489 (m), 1435 (w), 1366 (m), 1281 (m), 1150 (m), 1103 (m) cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ = 8.06 (d, *J* = 8.9, 1 H, H-9), 7.24 (s, br, 1 H, H-6), 7.06–7.00 (m, 1 H, H-8), 6.50–6.47 (m, 1 H, H-4), 2.61 (t, *J* = 7.5, 2 H, =CCH$_2$), 1.73 (quint, *J* = 7.5, 2 H, C*H*$_2$CH$_2$CH$_3$), 1.45 (hexuplet, *J* = 7.5, 2 H, C*H*$_2$CH$_3$), 0.98 (t, *J* = 7.5, 3 H, CH$_3$); ^{13}C NMR (125 MHz, CDCl$_3$): δ = 162.7, 158.9, 148.0, 145.5, 144.0, 123.5, 114.9, 113.8, 102.7, 96.6, 55.8, 32.8, 28.5, 22.1, 13.7; GC/MS: *m/z* = 272 (M$^+$, 100), 230 (20), 215 (15), 199 (11), 188 (19); HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for C$_{15}$H$_{17}$N$_2$O$_3$$^+$ 273.1234; Found: 273.1242.

3.3.5. 3-Butyl-7,8-dichloro-1*H*-benzo[4,5]imidazo[1,2-*c*][1,3]oxazin-1-one **2e**

Yield: 240 mg, starting from 367 mg of **1e** (77%) (Table 2, entry 5). Colorless solid, mp: 143–147 °C. IR (KBr): v = 1775 (s), 1667 (m), 1543 (w), 1435 (w), 1350 (m), 1134 (w), 1096 (m) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-*d$_6$*) δ = 8.18 (s, 1 H, H-6 or H-9), 8.07 (s, 1 H, H-9 or H-6), 6.91 (s, 1 H, H-4), 2.63 (t, *J* = 7.4, 2 H, =CCH$_2$), 1.65 (quint, *J* = 7.4, 2 H, =CCH$_2$C*H*$_2$), 1.40 (hexuplet, *J* = 7.4, 2 H, C*H*$_2$CH$_3$), 0.93 (t, *J* = 7.4, 3 H, CH$_3$); ^{13}C NMR (125 MHz, DMSO-*d$_6$*): δ = 163.9, 150.0, 143.5, 128.7, 128.3, 126.3, 120.5, 114.9, 96.3, 31.8, 27.9, 21.3, 13.5; GC/MS = 312 [(M + 2)$^+$, 61], 310 (M$^+$, 100), 268 (25), 253 (22), 226 (31), 202 (6); HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for C$_{14}$H$_{13}$Cl$_2$N$_2$O$_2$$^+$ 311.0349; Found: 311.0348.

3.3.6. 3-Butyl-8-nitro-1*H*-benzo[4,5]imidazo[1,2-*c*][1,3]oxazin-1-one **2f**

Yield: 129 mg, starting from 343 mg of **1f** (45%) (Table 2, entry 6). Colorless solid, mp: 165–168 °C; IR (KBr): v = 1775 (s), 1659 (m), 1543 (w), 1520 (m), 1343 (m), 748 (w) cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ = 9.05 (d, *J* = 1.9, 1 H, H-9), 8.39 (dd, *J* = 8.8, 1.9, 1 H, H-7), 7.83 (d, *J* = 8.8, 1 H, H-6), 6.63 (s, 1 H, H-4), 2.70 (t, *J* = 7.4, 2 H, =CCH$_2$), 1.76 (quint, *J* = 7.4, 2 H, C*H*$_2$CH$_2$CH$_3$), 1.49 (hexuplet, *J* = 7.4, 2 H, C*H*$_2$CH$_3$), 1.00 (t, *J* = 7.4, 3 H, CH$_3$); ^{13}C NMR (75 MHz, CDCl$_3$): δ = 165.6, 151.5, 148.6, 144.7, 143.2, 129.0, 122.1, 119.8, 111.0, 96.6, 33.1, 28.4, 22.1, 13.7; GC/MS: *m/z* = 287 (M$^+$, 100), 257 (11), 245 (49), 230 (27), 203 (23), 184 (16); HRMS (ESI-TOF) *m/z*: [M + Na + MeOH]$^+$ Calcd for C$_{15}$H$_{17}$N$_3$O$_5$Na$^+$ 342.1060; Found: 342.1064.

3.3.7. 3-Butyl-7-nitro-1*H*-benzo[4,5]imidazo[1,2-*c*][1,3]oxazin-1-one **2g**

Yield: 86 mg, starting from 343 mg of **1g** (30%) (Table 2, entry 7). Yellow solid, mp: 144–147 °C; IR (KBr): 1775 (s), 1667 (m), 1520 (s), 1350 (s), 1173 (w), 1119 (w), 934 (w), 833 (m), 741 (m) cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ = 8.62 (s, 1 H, H-6), 8.38–8.30 (m, 2 H, H-8 + H-9), 6.60 (s, 1 H, H-4), 2.68 (t, *J* = 7.4, 2 H, =CCH$_2$), 1.76 (quint, *J* = 7.4, 2 H, C*H*$_2$CH$_2$CH$_3$), 1.49 (hexuplet, *J* = 7.4, 2 H, C*H*$_2$CH$_3$), 1.00 (t, *J* = 7.4, 3 H, CH$_3$); ^{13}C NMR (75 MHz, DMSO-*d$_6$*): δ = 164.7, 150.1, 146.4, 144.2, 143.5, 133.5, 120.2, 115.8, 114.7, 96.5, 33.0,

28.4, 22.1, 13.7; GC/MS: *m/z* = 287 (M$^+$, 100), 245 (50), 230 (29), 203 (31), 184 (13); HRMS (ESI-TOF) *m/z*: [M + Na + MeOH]$^+$ Calcd for C$_{15}$H$_{17}$N$_3$O$_5$Na$^+$ 342.1060; Found: 342.1064.

3.3.8. 3-Octyl-1*H*-benzo[4,5]imidazo[1,2-*c*][1,3]oxazin-1-one **2h**

Yield: 254 mg, starting from 354 mg of **1h** (85%) (Table 2, entry 8). Colorless solid, mp: 90–94 °C; IR (KBr): ν = 1759 (s), 1667 (m), 1551 (m), 1396 (m), 1373 (m), 1134 (m), 1103 (m), 964 (w), 756 (m) cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$): δ = 8.24–8.17 (m, 1 H, aromatic), 7.83–7.75 (m, 1 H, aromatic), 7.50–7.39 (m, 2 H, aromatic), 6.70 (s, 1 H, H-4), 2.62 (t, *J* = 7.6, 2 H, =CC*H$_2$*), 1.74 (quint, *J* = 7.6, 2 H, =CCH$_2$C*H$_2$*), 1.48–1.18 [m, 10 H, (C*H$_2$*)$_5$CH$_3$], 0.89 (t, *J* = 7.0, 3 H, CH$_3$); ^{13}C NMR (75 MHz, CDCl$_3$): δ = 163.4, 147.8, 143.9, 143.5, 129.1, 126.4, 125.1, 119.5, 114.6, 96.4, 33.2, 31.8, 29.2, 29.1, 28.9, 26.4, 22.6, 14.1; GC/MS = 298 (M$^+$, 85), 283 (2), 269 (4), 255 (5), 239 (5), 225 (14), 213 (100), 200 (87), 185 (40), 171 (11), 158 (61), 130 (20); HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for C$_{18}$H$_{23}$N$_2$O$_2$$^+$ 299.1754; Found: 299.1757.

3.3.9. 3-Isopentyl-1*H*-benzo[4,5]imidazo[1,2-*c*][1,3]oxazin-1-one **2i**

Yield: 210 mg, starting from 312 mg of **1i** (82%) (Table 2, entry 9). Colorless solid, mp: 102–104°C; IR (KBr): ν = 1751 (s), 1667 (m), 1551 (w), 1451 (w), 1366 (s), 1134 (m), 1103 (m), 964 (w), 849 (w), 748 (m) cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$): δ = 8.21–8.15 (m, 1 H, aromatic), 7.77–7.72 (m, 1 H, aromatic), 7.50–7.37 (m, 2 H, aromatic), 6.48 (s, 1 H, H-4), 2.65–2.55 (m, 2 H, =CC*H$_2$*), 1.73–1.56 (m, 3 H, CH$_2$CH), 0.96 (d, *J* = 6.2, 6 H, 2 CH$_3$); ^{13}C NMR (75 MHz, CDCl$_3$): δ = 163.1, 147.4, 144.11, 144.03, 129.3, 126.2, 124.9, 119.7, 114.5, 96.5, 35.3, 31.1, 27.6, 22.3; GC/MS = 256 (M$^+$, 100), 241 (6), 227 (2), 214 (10), 200 (56), 185 (25), 171 (5), 158 (61), 143 (4), 130 (14); HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for C$_{15}$H$_{17}$N$_2$O$_2$$^+$ 257.1285; Found: 257.1286.

3.3.10. 3-Phenethyl-1*H*-benzo[4,5]imidazo[1,2-*c*][1,3]oxazin-1-one **2j**

Yield: 232 mg, starting from 346 mg of **1j** (80%) (Table 2, entry 10). Colorless solid, mp: 159–162 °C; IR (KBr): ν = 1767 (s), 1667 (m), 1558 (w), 1451 (w), 1360 (s), 1103 (m), 988 (m), 864 (m), 756 (s), 694 (s) cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$): δ = 8.25–8.17 (m, 1 H, aromatic), 7.81–7.72 (m, 1 H, aromatic), 7.53–7.40 (m, 2 H aromatic), 7.35–7.13 (m, 5 H, Ph), 6.45 (s, 1 H, H-4), 3.06 (dist t, *J* = 7.6, 2 H, CH$_2$), 2.92 (dist, *J* = 7.6, 2 H, CH$_2$); ^{13}C NMR (75 MHz, CDCl$_3$): δ = 161.4, 147.1, 144.0, 143.9, 139.2, 129.3, 128.7, 128.2, 126.7, 126.3, 125.0, 119.8, 114.6, 97.3, 34.8, 32.5; GC/MS = 290 (M$^+$, 34), 245 (1), 199 (7), 185 (2), 155 (5), 129 (3), 102 (4), 91 (100); HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for C$_{18}$H$_{15}$N$_2$O$_2$$^+$ 291.1128; Found: 291.1126.

3.3.11. 3-(Cyclohexylmethyl)-1*H*-benzo[4,5]imidazo[1,2-*c*][1,3]oxazin-1-one **2k**

Yield: 197 mg, starting from 338 mg of **1k** (70%) (Table 2, entry 11). Colorless solid, mp: 135–138°C; IR (KBr): ν = 1767 (s), 1667 (m), 1559 (w), 1451 (w), 1389 (m), 1366 (m), 1096 (w), 964 (w), 748 (m) cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ = 8.21 (d, *J* = 7.7, 1 H, aromatic), 7.77 (d, *J* = 8.1, 1 H, aromatic), 7.52–7.40 (m, 2 H, aromatic), 6.49 (s, 1 H, H-4), 2.48 (d, *J* = 7.0, 2 H, =CC*H$_2$*), 1.93–1.62 (m, 6 H, cyclohexyl), 1.39–0.96 (m, 5 H, cyclohexyl); ^{13}C NMR (125 MHz, CDCl$_3$): δ = 161.6, 147.3, 144.2, 129.4, 126.3, 124.9, 119.8, 114.6, 97.7, 41.0, 35.8, 33.0, 26.2, 26.0; GC/MS: *m/z* = 282 (M$^+$, 67), 200 (100), 156 (24), 129 (5); HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for C$_{17}$H$_{19}$N$_2$O$_2$$^+$ 283.1441; Found: 283.1448.

3.3.12. 3-(Cyclohex-1-en-1-yl)-1*H*-benzo[4,5]imidazo[1,2-*c*][1,3]oxazin-1-one **2l**

Yield: 176 mg, starting from 322 mg of **1l** (66%) (Table 2, entry 12). Colorless solid, mp: 191–195 °C; IR (KBr): ν = 1767 (s), 1636 (m), 1420 (w), 1366 (m), 1281 (w), 1180 (w), 1111 (m), 1026 (w), 833 (w), 748 (m) cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ = 8.24–8.16 (m, 1 H, aromatic), 7.81–7.71 (m, 1 H, aromatic), 7.53–7.39 (m, 2 H, aromatic), 7.00–6.90 (m, 1 H, =CH), 6.55 (s, 1 H, H-4), 2.40–2.24 (m, 4 H, cyclohexenyl), 1.86–1.74 (m, 2 H, cyclohexenyl), 1.74–1.62 (m, 2 H, cyclohexenyl); ^{13}C NMR (75 MHz, CDCl$_3$): δ = 157.7, 148.1, 144.5, 143.6, 134.0, 129.5, 127.1, 126.2, 124.9, 119.6, 114.5, 92.8, 25.9, 23.9, 22.0, 21.5; GC/MS = 266

(M^+, 100), 237 (7), 221 (23), 185 (26), 157 (9); HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{15}N_2O_2^+$ 267.1128; Found: 267.1129.

3.3.13. 3-(Methoxymethyl)-1*H*-benzo[4,5]imidazo[1,2-*c*][1,3]oxazin-1-one **2m**

Yield: 138 mg, starting from 286 mg of **1m** (60%) (Table 2, entry 13). Yellow solid, mp: 122–125°C; IR (KBr): v = 1751 (s), 1667 (m), 1558 (m), 1443 (m), 1381 (s), 1173 (m), 1103 (s), 957 (w), 748 (s) cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ = 8.23–8.18 (m, 1 H, aromatic), 7.82–7.75 (m, 1 H, aromatic), 7.53–7.43 (m, 2 H, aromatic), 6.81–6.78 (m, 1 H, H-4), 4.35 (s, 2 H, C*H*$_2$OCH$_3$), 3.53 (s, 3 H, OCH$_3$); ^{13}C NMR (125 MHz, CDCl$_3$): δ = 158.2, 146.8, 144.1, 143.5, 129.4, 126.4, 125.3, 120.0, 114.6, 97.2, 69.6, 59.4; GC/MS: *m/z* = 230 (M^+, 89), 199 (5), 185 (100), 171 (10), 157 (48), 129 (8); HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{12}H_{11}N_2O_3^+$ 231.0764; Found: 231.0768.

3.3.14. Methyl 3-(1-oxo-1*H*-benzo[4,5]imidazo[1,2-*c*][1,3]oxazin-3-yl)propanoate **2n**

Yield: 201 mg, starting from 328 mg of **1n** (74%) (Table 2, entry 14). Colorless solid, mp: 189–193°C; IR (KBr): v = 1767 (s), 1736 (s), 1667 (m), 1435 (w), 1366 (w), 1173 (m), 996 (m), 895 (w), 841 (w), 772 (m) cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ = 8.19 (d, *J* = 7.7, 1 H, aromatic), 7.77 (d, *J* = 8.1, 1 H, aromatic), 7.51–7.41 (m, 2 H, aromatic), 6.58 (s, 1 H, H-4), 3.72 (s, 3 H, CO$_2$CH$_3$), 2.97 (t, *J* = 7.2, 2 H, =CCH$_2$), 2.79 (t, *J* = 7.2, 2 H, C*H*$_2$CO$_2$CH$_3$); ^{13}C NMR (125 MHz, CDCl$_3$): δ = 171.8, 160.4, 147.0, 144.1, 143.7, 126.4, 125.2, 119.9, 114.6, 97.5, 52.1, 30.5, 28.4; GC/MS: *m/z* = 272 (M^+, 61), 243 (15), 212 (100), 199 (35), 185 (33), 169 (20), 157 (35); HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{14}H_{13}N_2O_4^+$ 273.0870; Found: 273.0874.

3.3.15. 3-(2-(*tert*-Butoxy)ethyl)-1*H*-benzo[4,5]imidazo[1,2-*c*][1,3]oxazin-1-one **2o′**

Yield: 189 mg, starting from 286 mg of **1o** (66%) (Table 2, entry 15). Colorless solid, mp: 189–193°C; IR (KBr): v = 1774 (s), 1666 (m), 1551 (w), 1389 (w), 1366 (m), 1204 (w), 1111 (w), 1080 (m), 756 (m) cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ = 8.25–8.21 (m, 1 H, aromatic), 7.82–7.77 (m, 1 H, aromatic), 7.52–7.42 (m, 2 H, aromatic), 6.65 (dist t, *J* = 0.8, 1 H, H-4), 3.73 (t, *J* = 6.1, 2 H, CH$_2$Ot-Bu), 2.83 (td, *J* = 6.1, 0.8, 2 H, =CCH$_2$), 1.20 (s, 9 H,); ^{13}C NMR (125 MHz, CDCl$_3$): δ = 160.5, 147.4, 144.2, 144.0, 129.4, 126.3, 125.0, 119.8, 114.6, 98.0, 73.5, 57.7, 34.5, 27.4; GC/MS: *m/z* = 286 (M^+, 21), 213 (12), 200 (100), 171 (16), 156 (22); HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{19}N_2O_3^+$ 287.1390; Found: 287.1395.

3.3.16. 2-(Hex-1-yn-1-yl)-6-nitro-1*H*-benzo[*d*]imidazole **3f**

Yield: 49 mg, starting from 343 mg of **1f** (20%) (Table 2, entry 6). Colorless solid, mp: 138–140 °C; IR (KBr): v = 2230 (w), 1520 (s), 1474 (w), 1435 (w), 1343 (s), 1065 (w), 818 (m) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-*d*$_6$): δ = 8.41 (s, br, 1 H, H-3), 8.14 (dd, *J* = 8.9, 2.2, 1 H, H-5), 7.69 (d, *J* = 8.9, 1 H, H-4), 2.58 (t, *J* = 7.2, 2 H, ≡CCH$_2$), 1.60 (quint, *J* = 7.2, 2 H, C*H*$_2$CH$_2$CH$_3$), 1.49 (hexuplet, *J* = 7.2, 2 H, C*H*$_2$CH$_3$), 0.95 (t, *J* = 7.2, 3 H, CH$_3$) (Note: the NH signal was incorporated into the broad HOD signal at 3.49 ppm); ^{13}C NMR (125 MHz, DMSO-*d*$_6$): δ = 143.1, 139.6, 118.3, 114.3 (br), 95.8, 71.6, 29.5, 21.4, 18.1, 13.3; GC/MS: *m/z* = 243 (M^+, 100), 228 (48), 214 (73), 201 (93), 182 (41), 168 (54), 155 (57), 127 (27); HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{13}H_{14}N_3O_2^+$ 244.1081; Found: 244.1081.

3.3.17. 2-(Hex-1-yn-1-yl)-5-nitro-1*H*-benzo[*d*]imidazole **3g**

Yield: 75 mg, starting from 343 mg of **1g** (31%) (Table 2, entry 7). Yellow solid, mp: 145–148 °C; IR (KBr): v = 2237 (w), 1520 (s), 1474 (w), 1435 (w), 1366 (w), 1342 (s), 1065 (m), 818 (m), 741 (m) cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$): δ = 8.75 (s, 1 H, H-4), 8.29 (d, *J* = 8.8, 1 H, H-6), 7.83 (d, *J* = 8.8, 1 H, H-7), 2.48 (t, *J* = 7.3, 2 H, ≡CCH$_2$), 1.50 (quint, *J* = 7.3, 2 H, C*H*$_2$CH$_2$CH$_3$), 1.33 (hexuplet, *J* = 7.3, 2 H, C*H*$_2$CH$_3$), 0.78 (t, *J* = 7.3, 3 H, CH$_3$) (Note: the NH signal was too broad to be detected); ^{13}C NMR (125 MHz, CDCl$_3$): δ = 144.4, 140.4, 119.2, 115.1 (br), 112.6 (br), 98.2, 71.0, 29.9, 22.0, 19.1, 13.4; GC/MS: *m/z* = 243 (M^+, 100), 228 (44), 214 (71), 201 (96), 182 (40), 168 (54), 155 (56); HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{13}H_{14}N_3O_2^+$ 244.1081; Found: 244.1082.

4. Conclusions

In conclusion, we have reported that simple and inexpensive $ZnCl_2$ is able to promote the heterocyclization of *N*-Boc-2-alkynylbenzimidazoles under mild conditions (40 °C in CH_2Cl_2 for 3h), giving access to new polycyclic heterocycles, 1*H*-benzo[4,5]imidazo[1,2-*c*][1,3]oxazin-1-ones. While in the previous literature $ZnCl_2$ was reported to promote complete *N*-Boc deprotection with elimination of isobutene and CO_2, in the present process it assisted the 6-*endo-dig* heterocyclization of the carbamate intermediate with incorporation of the carbamate group into the final polyheterocyclic derivative. $ZnCl_2$ thus played a dual role, by promoting the Boc deprotection of the substrate with elimination of the *tert*-butyl carbonation (which could be trapped by substrates bearing a nucleophilic group) and activating the triple bond toward the intramolecular nucleophilic attack by the carbamate moiety. The benzimidazoxazinone derivatives have been obtained in moderate to high yields starting from differently substituted substrates, and the structure of representative products has been confirmed by X-ray diffraction analysis.

Supplementary Materials: The following are available online. Preparation and characterization of *N*-Boc-2-alkynylbenzimidazole substrates **1a**–**1o**, X-ray crystallographic data for products **2a**, **2c**, and **2f**, Copies of HRMS, ^{1}H NMR, and ^{13}CNMR spectra.

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References

1. Zheng, L.; Hua, R. Recent Advances in Construction of Polycyclic Natural Product Scaffolds via One-Pot Reactions Involving Alkyne Annulation. *Front. Chem.* **2020**, *8*, 580355. [CrossRef]
2. Hong, F.-L.; Ye, L.-W. Transition Metal-Catalyzed Tandem Reactions of Ynamides for Divergent N-Heterocycle Synthesis. *Acc. Chem. Res.* **2020**, *53*, 2003–2019. [CrossRef] [PubMed]
3. Kaur, N.; Verma, Y.; Grewal, P.; Ahlawat, N.; Bhardwaj, P.; Jangid, N.K. Palladium acetate assisted synthesis of five-membered *N*-polyheterocycles. *Synth. Commun.* **2020**, *50*, 1567–1621. [CrossRef]
4. Gabriele, B.; Mancuso, R.; Veltri, L.; Ziccarelli, I.; Della Ca', N. Palladium-Catalyzed Double Cyclization Processes Leading to Polycyclic Heterocycles: Recent Advances. *Eur. J. Org. Chem.* **2019**, *2019*, 5073–5092. [CrossRef]
5. Wang, R.; Xie, X.; Liu, H.; Zhou, Y. Rh(III)-Catalyzed C–H Bond Activation for the Construction of Heterocycles with *sp*^{3}-Carbon Centers. *Catalysts* **2019**, *9*, 823. [CrossRef]
6. Ghosh, A.; Carter, R.G. Recent Syntheses and Strategies toward Polycyclic Gelsemium Alkaloids. *Angew. Chem. Int. Ed.* **2019**, *58*, 681–694. [CrossRef]
7. Passador, K.; Thorimbert, S.; Botuha, C. Heteroaromatic Rings of the Future': Exploration of Unconquered Chemical Space. *Synthesis* **2019**, *51*, 384–398.
8. Hyland, I.K.; O'Toole, R.F.; Smith, J.A.; Bissember, A.C. Progress in the Development of Platelet-Activating Factor Receptor (PAFr) Antagonists and Applications in the Treatment of Inflammatory Diseases. *ChemMedChem* **2018**, *13*, 1873–1884. [CrossRef]
9. Hemmerling, F.; Hahn, F. Biosynthesis of oxygen and nitrogen-containing heterocycles in polyketides. *Beilstein J. Org. Chem.* **2016**, *12*, 1512–1550. [CrossRef]
10. Shokova, E.A.; Kovalev, V.V. Biological Activity of Adamantane-Containing Mono- and Polycyclic Pyrimidine Derivatives (A Review). *Pharm. Chem. J.* **2016**, *50*, 63–75. [CrossRef]

11. Fizer, M.; Slivka, M. Synthesis of [1,2,4]triazolo[1,5-*a*]pyrimidine (microreview). *Chem. Heterocycl. Compds.* **2016**, *52*, 155–157. [CrossRef]

12. Li, J.; Yang, F.; Hu, W.; Ren, B.; Chen, Z.-S.; Ji, K. Gold(I)-catalyzed tandem cyclization of cyclopropylidene-tethered propargylic alcohols: An approach to functionalized naphtho[2,3-*c*]pyrans. *Chem. Commun.* **2020**, *56*, 9154–9157. [CrossRef] [PubMed]

13. He, Y.; Li, Z.; Robyens, K.; Van Meervelt, L.; Van der Eycken, R.V. A Gold-Catalyzed Domino Cyclization Enabling Rapid Construction of Diverse Polyheterocyclic Frameworks. *Angew. Chem. Int. Ed.* **2018**, *57*, 272–276. [CrossRef]

14. Alcaide, B.; Almendros, P.; Fernández, I.; Herrea, F.; Luna, A. Gold-Catalyzed Divergent Ring-Closing Modes of Indole-Tethered Amino Allenynes. *Chem. Eur. J.* **2018**, *24*, 1448–1454. [CrossRef]

15. Li, Z.; Song, L.; Van Meervelt, L.; Tian, G.; Van der Eycken, E.V. Cationic Gold(I)-Catalyzed Cascade Bicyclizations for Divergent Synthesis of (Spiro)polyheterocycles. *ACS Catal.* **2018**, *8*, 6388–6393. [CrossRef]

16. Zhang, J.-h.; Wei, Y.; Shi, M. Gold-catalyzed ring enlargement and cycloisomerization of alkynylamide tethered alkylidenecyclo-propanes. *Org. Chem. Front.* **2018**, *5*, 2980–2985. [CrossRef]

17. Ito, M.; Kawasaki, R.; Kanyiva, K.S.; Shibata, T. Construction of a Polycyclic Conjugated System Containing a Dibenzazepine Moiety by Cationic Gold(I)-Catalyzed Cycloisomerization. *Eur. J. Org. Chem.* **2016**, *2016*, 5234–5237. [CrossRef]

18. Kumar, R.; Arigela, R.K.; Samala, S.; Kundu, B. Diversity Oriented Synthesis of Indoloazepinobenzimidazole and Benzimidazotri-azolobenzodiazepine from N^1-Alkyne-1,2-diamines. *Chem. Eur. J.* **2015**, *21*, 18828–18833. [CrossRef]

19. Chen, M.; Sun, N.; Xu, W.; Zhao, J.; Wang, G.; Liu, Y. Gold-Catalyzed Ring Expansion of Alkynyl Heterocycles through 1,2-Migration of an Endocyclic Carbon–Heteroatom Bond. *Chem. Eur. J.* **2015**, *21*, 18571–18575. [CrossRef] [PubMed]

20. Zheng, Y.; Bao, M.; Yao, R.; Qiu, L.; Xu, X. Palladium-catalyzed carbene/alkyne metathesis with enynones as carbene precursors: Synthesis of fused polyheterocycles. *Chem. Commun.* **2018**, *54*, 350–353. [CrossRef] [PubMed]

21. Feng, Y.; Tian, N.; Li, Y.; Jia, C.; Li, X.; Wang, L.; Ciu, X. Construction of Fused Polyheterocycles through Sequential [4 + 2] and [3 + 2] Cycloadditions. *Org. Lett.* **2017**, *19*, 1658–1661. [CrossRef]

22. Kumar, S.; Saunthwal, R.K.; Aggarwal, T.; Kotla, S.K.R.; Verma, A.K. Palladium meets copper: One-pot tandem synthesis of pyrido fused heterocycles *via* Sonogashira conjoined electrophilic cyclization. *Org. Biomol. Chem.* **2016**, *14*, 9063–9071. [CrossRef] [PubMed]

23. Dethe, D.H.; Boda, R. A Novel Pd-Catalysed Annulation Reaction for the Syntheses of Pyrroloindoles and Pyrroloquinolines. *Chem. Eur. J.* **2016**, *22*, 106–110. [CrossRef] [PubMed]

24. Wu, X.; Ji, H. Rhodium-Catalyzed [4 + 1] Cyclization via C–H Activation for the Synthesis of Divergent Heterocycles Bearing a Quaternary Carbon. *J. Org. Chem.* **2018**, *83*, 4650–4656. [CrossRef] [PubMed]

25. Youn, S.W.; Yoo, H.J. One-Pot Sequential N-Heterocyclic Carbene/Rhodium(III) Catalysis: Synthesis of Fused Polycyclic Isocoumarins. *Adv. Synth. Catal.* **2017**, *359*, 2176–2183. [CrossRef]

26. Ghorai, D.; Choudhury, J. Rhodium(III)–N-Heterocyclic Carbene-Driven Cascade C–H Activation Catalysis. *ACS Catal.* **2015**, *5*, 2692–2696. [CrossRef]

27. Kozak, J.A.; Dodd, J.M.; Harrison, T.J.; Jardine, K.J.; Patrick, B.O.; Dake, G.R. Enamides and Enesulfonamides as Nucleophiles: Formation of Complex Ring Systems through a Platinum(II)-Catalyzed Addition/Friedel−Crafts Pathway. *J. Org. Chem.* **2009**, *74*, 6929–6935. [CrossRef]

28. Marion, F.; Coulomb, J.; Servais, A.; Courillon, C.; Fensterbank, L.; Malacria, M. Radical cascade cyclizations and platinum(II)-catalyzed cycloisomerizations of ynamides. *Tetrahedron* **2006**, *62*, 3856–3871. [CrossRef]

29. Mamane, V.; Hannen, P.; Fürstner, A. Synthesis of Phenanthrenes and Polycyclic Heteroarenes by Transition-Metal Catalyzed Cycloisomerization Reactions. *Chem. Eur. J.* **2004**, *10*, 4556–4575. [CrossRef]

30. Ghosh, K.; Shankar, M.; Rit, R.K.; Dubey, G.; Bharatam, P.V.; Sahoo, A.K. Sulfoximine-Assisted One-Pot Unsymmetrical Multiple Annulation of Arenes: A Combined Experimental and Computational Study. *J. Org. Chem.* **2018**, *83*, 9667–9681. [CrossRef]

31. Miclo, Y.; Garcia, P.; Evanno, Y.; George, P.; Sevrin, M.; Malacria, M.; Gandon, V.; Aubert, C. Synthesis of Orthogonally Protected Angular Nitrogen Polyheterocycles via CpCo-Catalyzed Pyridine Formation. *Synlett* **2010**, *2010*, 314–2318.

32. Hoshimoto, Y.; Ashida, K.; Sasaoka, Y.; Kumar, R.; Kamikawa, K.; Verdaguer, X.; Riera, A.; Ohashi, M.; Ogoshi, S. Efficient Synthesis of Polycyclic γ-Lactams by Catalytic Carbonylation of Ene-Imines via Nickelacycle Intermediates. *Angew. Chem. Int. Ed.* **2017**, *56*, 8206–8210. [CrossRef] [PubMed]

33. Liu, X.; Wang, Z.-S.; Zhai, T.-Y.; Luo, C.; Zhang, Y.-P.; Chen, Y.-B.; Deng, C.; Liu, R.-S.; Ye, L.-W. Copper-Catalyzed Azide–Ynamide Cyclization to Generate α-Imino Copper Carbenes: Divergent and Enantioselective Access to Polycyclic N-Heterocycles. *Angew. Chem. Int. Ed.* **2020**, *59*, 17984–17990. [CrossRef] [PubMed]

34. Mao, X.-F.; Zhu, X.-P.; Li, D.-Y.; Liu, P.-N. Cu-Catalyzed Cascade Annulation of Alkynols with 2-Azidobenzaldehydes: Access to 6*H*-Isochromeno[4,3-*c*]quinolone. *J. Org. Chem.* **2017**, *82*, 7032–7039. [CrossRef] [PubMed]

35. Ho, H.E.; Oniwa, K.; Yamamoto, Y.; Jin, T. *N*-Methyl Transfer Induced Copper-Mediated Oxidative Diamination of Alkynes. *Org. Lett.* **2016**, *18*, 2487–2490. [CrossRef] [PubMed]

36. Mandadapu, A.K.; Sharma, S.K.; Gupta, S.; Krishna, D.G.V.; Kundu, B. Unprecedented Cu-Catalyzed Coupling of Internal 1,3-Diynes with Azides: One-Pot Tandem Cyclizations Involving 1,3-Dipolar Cycloaddition and Carbocyclization Furnishing Naphthotriazoles. *Org. Lett.* **2011**, *13*, 3162–3165. [CrossRef] [PubMed]

37. Bakholdina, A.; Lukin, A.; Bakulina, O.; Guranova, N.; Krasavin, M. Dual use of propargylamine building blocks in the construction of polyheterocyclic scaffolds. *Tetrahedron Lett.* **2020**, *61*, 151970. [CrossRef]

38.   Habert, L.; Sallio, R.; Durandetti, M.; Gosmini, C.; Gillaizeau, I. Zinc Chloride Mediated Synthesis of 3*H*-Oxazol-2-one and Pyrrolo-oxazin-1-one from Ynamide. *Eur. J. Org. Chem.* **2019**, *2019*, 5175–5179. [CrossRef]

39.   Muralidhar, B.; Reddy, S.R. Zn(II) Chloride Promoted Benzannulation Strategy for One-Pot Regioselective Synthesis of 6*H*-Benzo[*c*]chromenes. *ChemistrySelect* **2017**, *2*, 2539–2543. [CrossRef]

40.   Li, L.; Zhou, B.; Wang, Y.-H.; Shu, C.; Pan, Y.-F.; Lu, X.; Ye, L.-W. Zinc-Catalyzed Alkyne Oxidation/C-H Functionalization: Highly Site-Selective Synthesis of Versatile Isoquinolones and β-Carbolines. *Angew. Chem. Int. Ed.* **2015**, *54*, 8245–8249. [CrossRef]

41.   Kim, H.; Tung, T.T.; Park, S.B. Privileged Substructure-Based Diversity-Oriented Synthesis Pathway for Diverse Pyrimidine-Embedded Polyheterocycles. *Org. Lett.* **2013**, *15*, 5814–5817. [CrossRef]

42.   Liu, Y.; Zhen, W.; Dai, W.; Wang, F.; Li, X. Silver(I)-Catalyzed Addition-Cyclization of Alkyne-Functionalized Azomethines. *Org. Lett.* **2013**, *15*, 874–877. [CrossRef]

43.   Yamamoto, Y.; Nishiyama, M.; Imagawa, H.; Nishizawa, M. Hg(OTf)$_2$-Catalyzed cyclization of alkynyl *tert*-butylcarbonate leading to cyclic enol carbonate. *Tetrahedron Lett.* **2006**, *47*, 8369–8373. [CrossRef]

44.   Krishnan, K.K.; Ujwaldev, S.M.; Saranya, S.; Anilkumar, G.; Beller, M. Recent Advances and Perspectives in the Synthesis of Heterocycles via Zinc Catalysis. *Adv. Synth. Catal.* **2019**, *361*, 382–404. [CrossRef]

45.   Saranya, S.; Harry, N.A.; Ujwaldev, S.M.; Anilkumar, G. Recent Advances and Perspectives on the Zinc-Catalyzed Nitroaldol (Henry) Reaction. *Asian J. Org. Chem.* **2017**, *6*, 1349–1360. [CrossRef]

46.   Thankachan, A.P.; Asha, S.; Sindhu, K.S.; Anilkumar, G. An overview of Zn-catalyzed enantioselective aldol type C-C bond formation. *RSC Adv.* **2015**, *5*, 62179–62193. [CrossRef]

47.   Wu, X.-F. Non-Redox-Metal-Catalyzed Redox Reactions: Zinc Catalysts. *Chem. Asian J.* **2012**, *7*, 2502–2509. [CrossRef]

48.   Wu, X.-F.; Neumann, H. Zinc-Catalyzed Organic Synthesis: C-C, C-N, C-O Bond Formation Reactions. *Adv. Synth. Catal.* **2012**, *354*, 3141–3160. [CrossRef]

49.   Wutts, P.G.M. *Greene's Protective Groups in Organic Synthesis*, 5th ed.; John Wiley & Sons, Inc.: Hoboken, NJ, USA, 2014; pp. 755–939.

50.   Langille, E.; Bottaro, C.S.; Drouin, A. A novel use of catalytic zinc-hydroxyapatite columns for the selective deprotection of *N*-tert-butyloxycarbonyl (BOC) protecting group using flow chemistry. *J. Flow Chem.* **2020**, *10*, 377–387. [CrossRef]

51.   Vu, H.-D.; Renault, J.; Roisnel, T.; Robert, C.; Jéhan, P.; Gouault, N.; Uriac, P. Reactivity of *N*-Boc-Protected Amino-Ynones in the Presence of Zinc Chloride: Formation of Acetylenic Cyclic Imines and Their Palladium Complexes. *Eur. J. Org. Chem.* **2015**, *2015*, 4868–4875. [CrossRef]

52.   Nigam, S.C.; Mann, A.; Taddei, M.; Wermuth, C.-G. Selective Removal of the Tert-Butoxycarbonyl Group from Secondary Amines: ZnBr$_2$ as the Deprotecting Reagent. *Synth. Commun.* **1989**, *19*, 3139–3142. [CrossRef]

53.   Wu, Y.-Q.; Limburg, D.C.; Wilkinson, D.E.; Vaal, M.J.; Hamilton, G.S. A mild deprotection procedure for *tert*-butyl esters and *tert*-butyl ethers using ZnBr$_2$ in methylene chloride. *Tetrahedron Lett.* **2000**, *41*, 2847–2849. [CrossRef]

54.   Kaul, R.; Brouillette, Y.; Sajjadi, Z.; Hansford, K.A.; Lubell, W.D. Selective *tert*-Butyl Ester Deprotection in the Presence of Acid Labile Protecting Groups with Use of ZnBr$_2$. *J. Org. Chem.* **2004**, *69*, 6131–6133. [CrossRef] [PubMed]