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Research article

Catalytic coupling of 1-(2-(allyloxy)phenyl)-2-yn-1-ols and isonitriles for the synthesis of 2-(benzofuran-2-yl)acetamides: A combined experimental and theoretical study

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ABSTRACT

A new catalytic approach to the synthesis of an important sub-class of benzofuran derivatives (namely, 2-(benzofuran-2-yl)acetamides, known to possess significant biological activities) has been developed. The new method is based on the use of $Pd(PPh_3)_4$ as simple and commercially available catalyst, readily prepared 1-(2-(allyloxy)phenyl)-2-yn-1-ols, and commercially available isonitriles. Formation of benzofuran-2-yl)acetamides derives from a mechanistic pathway involving an ordered sequence of steps, that are, oxidative addition of the phenoxyallyl moiety to Pd(0), isonitrile insertion, water attack to the ensuing (allyl)(imidoyl)palladium complex, β-H elimination from the H-O-C-Pd(allyl) moiety with formation of an allylpalladium hydride species and a 2-(3-hydroxybenzofuran-2(3*H*)-ylidene)acetamide intermediate, followed by reduction of the latter by (allyl)PdH and MeOH. This mechanistic proposal has been corroborated by DFT studies, while the structures of representative products have been confirmed by X-ray diffraction analysis.

1. Introduction

The palladium-catalyzed coupling of isonitriles (isocyanides) and organic substrates is an important process, which leads to the formation of functionalized compounds in one step starting from simple and readily available feedstocks (for reviews, see references [1–5]). The isonitrile group, being isoelectronic with carbon monoxide, in a similar manner as CO [6] is able to insert into the palladium-carbon bond arising from the oxidative addition of a suitable substrate to Pd(0). This leads to the formation of an imidoylpalladium intermediate, which may couple with a nucleophile with formation of the final product bearing an imino moiety and with regeneration of the catalyst. As shown in Scheme 1a, the most commonly employed substrates for this kind of process, called imidoylative coupling, are organic halides that can oxidatively add to Pd(0) in an efficient manner [1–5].

Several intramolecular versions of this reactivity have been reported in the literature, which have led to the formation of a plethora of heterocyclic derivatives, as exemplified in Scheme 1b (for reviews, see references [7,8]. To the best of our knowledge, however, a process in which isonitrile insertion occurs after oxidative addition of an allyloxyphenyl moiety to Pd(0) followed by intramolecular triple bond insertion has not been previously reported. In this work, we disclose the first example of this kind of reactivity, which leads to the formation of high value added 2-(benzofuran-2-yl)acetamides **3** in one synthetic step starting from simple and readily available building blocks (isonitriles **2** and 1-(2-(allyloxy)phenyl)-2-yn-1-ols **1**), under the catalytic action of commercially available $Pd(PPh_3)_4$ (Scheme 1d). The synthesized products **3** belong to a particularly important sub-class of benzofuran

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derivatives, and are known to possess antifungal [9] and anticonvulsant [10–13] activities. Although several methods have been reported in the literature for their production (for recent examples, see references [9,14–23]), mainly based on functionalization of benzofuran derivatives [9,14–21], to the best of our knowledge only one approach based on catalytic activation of isonitriles has been reported so far, which concerned the use of 2-(1-hydroxyprop-2-yn-1-yl)phenols as coupling partners under basic conditions (Scheme 1c) [22]. However, that method was limited to the use of substrates bearing an external triple bond, and the catalytic pathway (involving Pd(II) as the active catalytic species under basic conditions) was completely different from that followed in the our present reaction, catalyzed by Pd(0) under neutral conditions (Scheme 1d).

2. Results and discussion

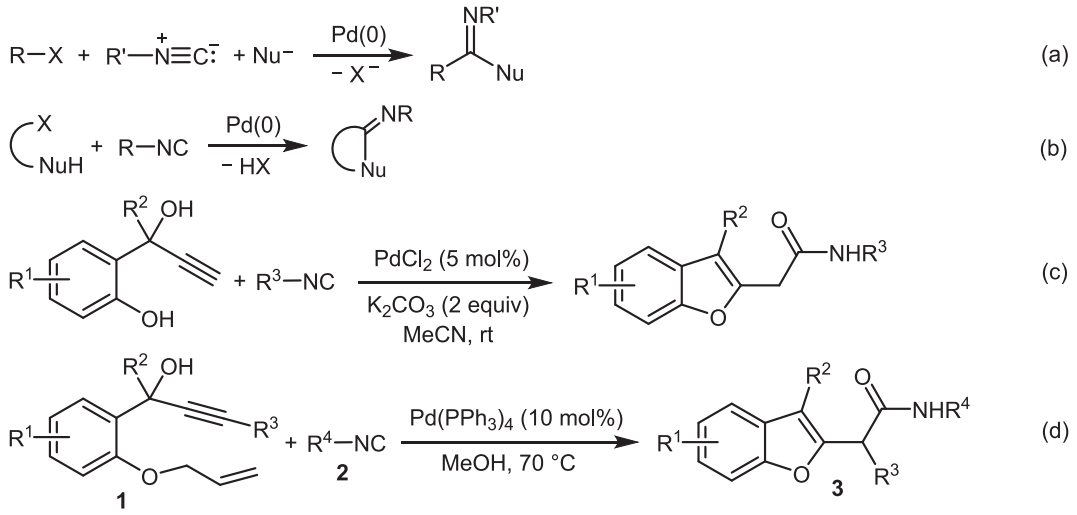
2.1. Synthesis of 2-(benzofuran-2-yl)acetamides 3 by $Pd(PPh_3)_4$-catalyzed coupling between 1-(2-(allyloxy)phenyl)-2-yn-1-ols 1 and isonitriles 2

To assess the possibility to realize a novel approach to the synthesis of 2-(benzofuran-2-yl)acetamides **3** using isonitriles **2** as source of the amido group, we decided to employ readily available 1-(2-(allyloxy)phenyl)-2-yn-1-ols **1** (easily synthesized by allylation of 1-(2-hydroxyphenyl) aldehydes or ketones followed by addition of alkynylmagnesium bromide [24]) as the coupling partners in the presence of Pd$(PPh_3)_4$ as Pd(0) source. It is in fact known that these substrates may oxidatively add to Pd(0) to give the corresponding (allyl)(phenoxy) palladium complex **I** [23,24] (Scheme 2; unreactive PPh_3 ligands are omitted for clarity). The latter would undergo intramolecular triple bond insertion to give intermediate **II**, followed by isonitrile insertion to give (allyl)(imidoyl)palladium complex **III**. Attack by water (present in the reaction mixture initially as impurity and then also formed during the dehydrative cyclization process) would then lead to tetrahedral intermediate **IV**, which undergoes β-H elimination from the H-O-C-Pd (allyl) moiety with formation of a 2-(3-hydroxybenzofuran-2(3*H*)-ylidene)acetamide intermediate **V** and an allylpalladium hydride species **VI**. According to a known reactivity [25,26], the latter species **V** and **VI** would then react with formation of the bis-allylpalladium complex **VII** with elimination of water. Finally, nucleophilic attack by MeOH (also used as solvent) would lead to the final product **3** together with 3-methoxy-1-propene (Scheme 2).

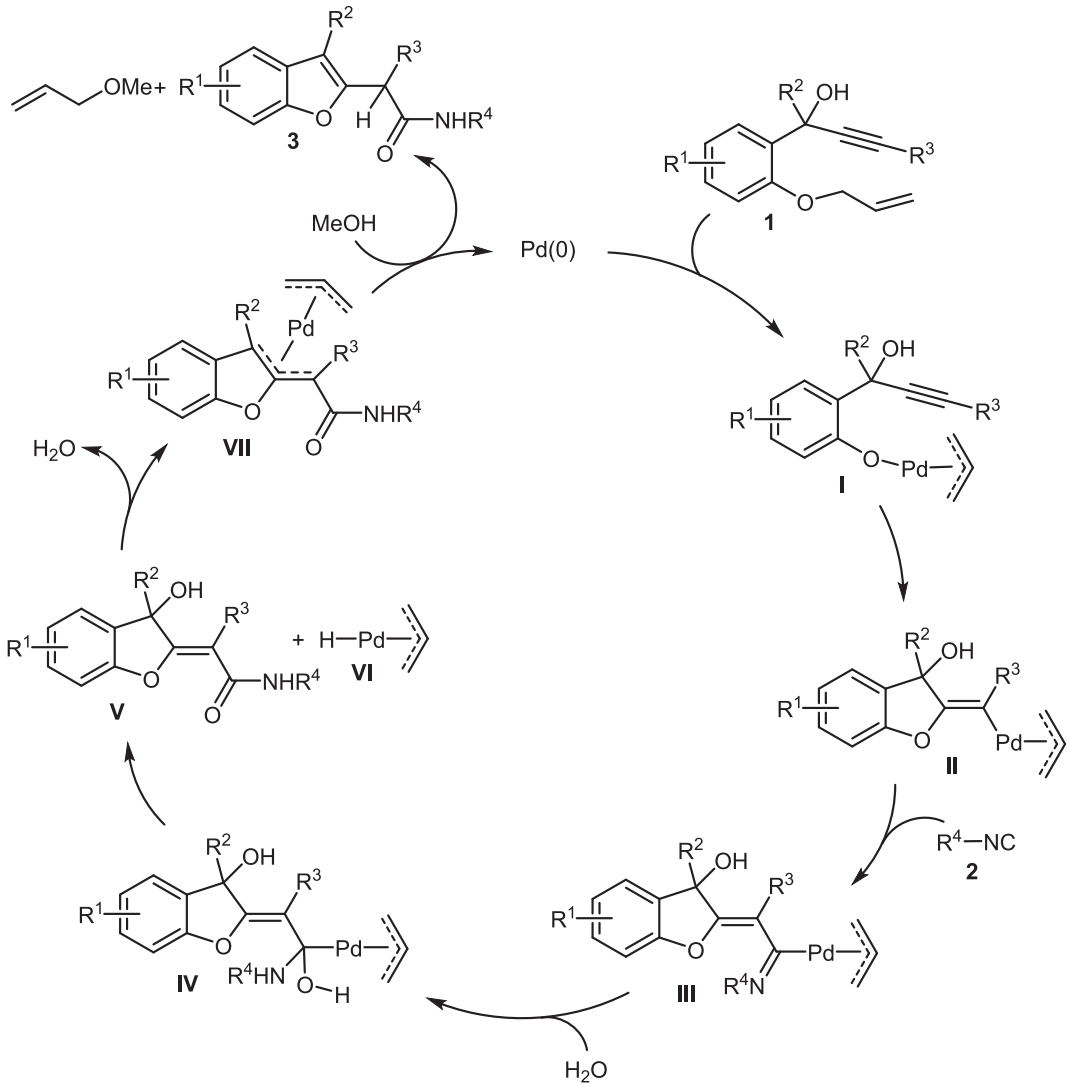
The first substrates we tested for validating our work hypothesis were 1-(2-(allyloxy)phenyl)hept-2-yn-1-ol **1a** and commercially available *tert*-butyl isocyanide **2a**. These compounds were allowed to react under nitrogen in MeOH at 100 °C in the presence of Pd$(PPh_3)_4$ and with a **2a**:**1a**:Pd$(PPh_3)_4$ molar ratio of 40:20:1 (initial concentration of **1a** = 0.15 mmol per mL of MeOH). After 15 h reaction time, **1a** substrate conversion was quantitative, and we were pleased to observe the formation of the desired 2-(benzofuran-2-yl)-*N*-(*tert*-butyl)hexanamide **3aa**, which, however, was isolated from the reaction mixture in modest yield (37 %; chromatographically immobile materials accounted for the remaining part of the converted substrate; Table 1, entry 1). To improve this encouraging but still unsatisfactory result, we performed a brief optimization study, as shown in Table 1, entries 2–9 In particular, we changed the **2a**:**1a**:Pd$(PPh_3)_4$ molar ratio and the reaction temperature. Under the optimized conditions, corresponding to 70 °C and **2a**:**1a**:Pd$(PPh_3)_4$ molar ratio of 10:10:1, with an initial **1a** concentration of 0.15 mmol per mL of MeOH, the desired product **3aa** could be isolated in 80 % yield after 5 h reaction time (Table 1, entry 8 and Table 2, entry 1). The results obtained from the optimization study seem to suggest that partial product decomposition took place by increasing the reaction temperature from 70 °C to 80 °C (Table 1, entry 5; yield of **3aa** = 65 %) or by prolonging the reaction time from 5 h to 15 h (Table 1, entry 4; yield of **3aa** = 48 %).

The structure of **3aa** was confirmed by XRD analysis (Fig. 1; see the Supporting Information for full XRD data). This compound is chiral, but it was obtained in racemic form, as our protocol is not enantioselective. On the other hand, to verify the formation of the alkoxypropene coproduct, as predicted by our mechanistic hypothesis shown in Scheme 2, we carried out an experiment in a higher alcohol, such as phenethyl alcohol. In fact, such an experiment would have led to the formation of (2-(allyloxy)ethyl)benzene, more easily detectable by GC–MS analysis than 3-methoxy-1-propene. As predicted, and in full agreement with our proposed mechanism (Scheme 2), the reaction of **1a** with **2a**, performed under the same optimized conditions as those of Table 1, entry 8, but in phenethyl alcohol instead of MeOH, led to the formation of **3aa** in 70 % isolated yield together with a 44 % yield of (2-(allyloxy)ethyl)benzene (Scheme 3; the difference in yield between the two products is due to the volatility of (2-(allyloxy)ethyl)benzene, which complicates its recovery from the reaction mixture).

We then assessed the generality of the process by applying the optimized conditions to differently substituted 1-(2-(allyloxy)phenyl)-2-yn-1-ols and to other commercially available isocyanides, in MeOH as

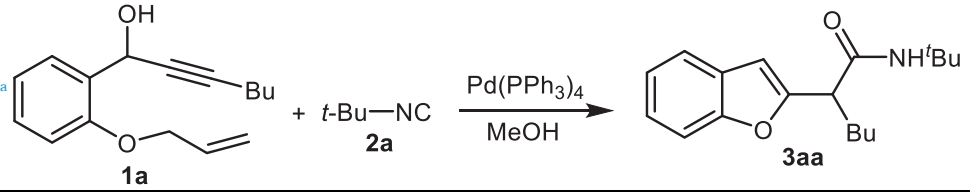


Scheme 1. (a) Pd(0)-catalyzed imidoylative coupling; (b) An intramolecular example of imidoylative coupling leading to heterocyclic derivatives; (c) Pd(II)-catalyzed coupling between 2-(1-hydroxyprop-2-yn-1-yl)phenols and isocyanides under basic conditions leading to 2-(benzofuran-2-yl)acetamides; (d) *This work:* Pd(0)-catalyzed coupling between 1-(2-(allyloxy)phenyl)-2-yn-1-ols **1** and isocyanides **2** leading to multi-substituted 2-(benzofuran-2-yl)acetamides **3** under neutral conditions.



Scheme 2. Mechanistic hypothesis leading to 2-(benzofuran-2-yl)acetamides **3** from 1-(2-(allyloxy)phenyl)-2-yn-1-ols **1** and isonitriles **2** under the catalysis of Pd(0).

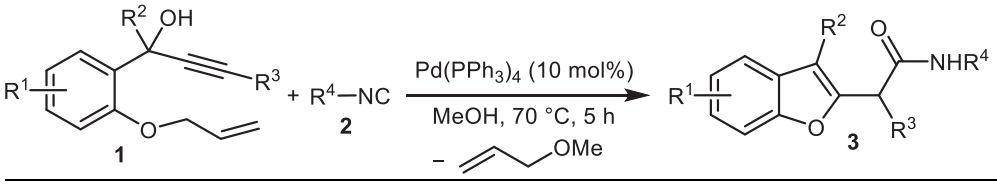
Table 1
$Pd(PPh_3)_4$-catalyzed coupling between 1-(2-(allyloxy)phenyl)hept-2-yn-1-ol **1a** and *tert*-butyl isocyanide **2a** to 2-(benzofuran-2-yl)-*N*-(*tert*-butyl)hexanamide **3aa** under different conditions.[a]

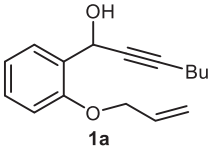
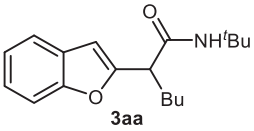
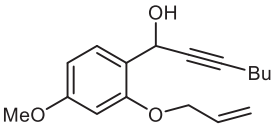
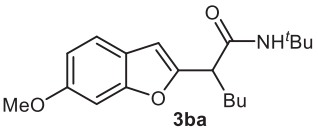
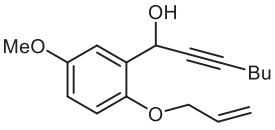
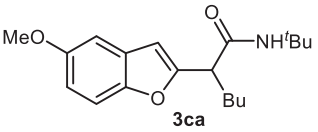
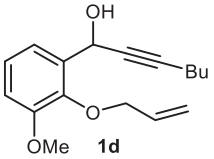
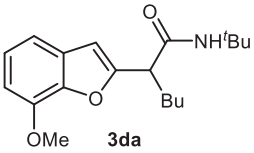
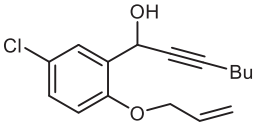
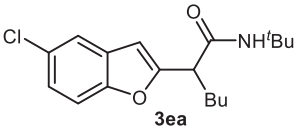
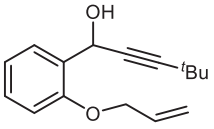
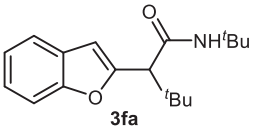
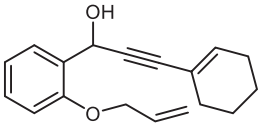
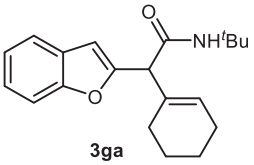
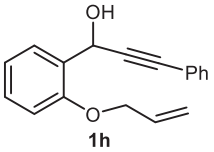
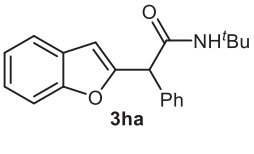
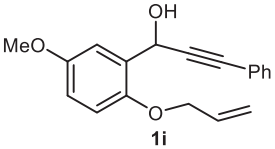
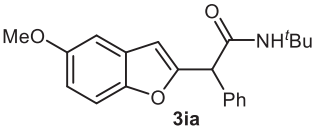


Entry	Pd:**1a**:**2a** molar ratio	Concn of **1a**[b]	T (°C)	t (h)	Yield (%) of **3aa**[c]
1	1:20:40	0.15	100	15	37
2	1:10:20	0.15	100	15	40
3	1:10:20	0.15	80	15	42
4	1:10:10	0.15	80	15	48
5	1:10:10	0.15	80	5	65
6	1:10:10	0.05	80	5	42
7	1:10:10	0.10	80	5	51
8	1:10:10	0.15	70	5	80
9	1:10:10	0.15	70	3	65[d]
10	1:20:20	0.15	70	8	69

[a] All reactions were carried out in MeOH as the solvent with $Pd(PPh_3)_4$ as catalyst. Unless otherwise noted, conversion of **1a** was quantitative.
[b] Mmol of **1a** per mL of MeOH.
[c] Isolated yield based on starting **1a**.
[d] Conversion of **1a** was incomplete (ca. 80%, by GLC).

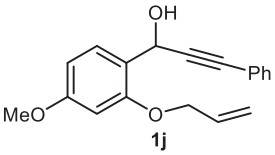
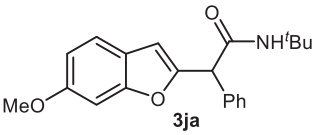
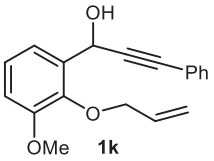
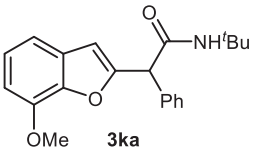
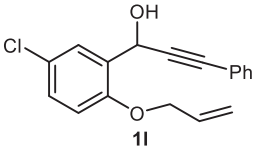
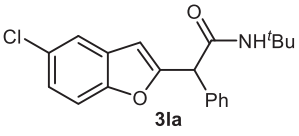
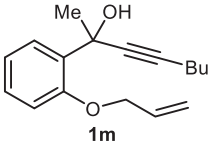
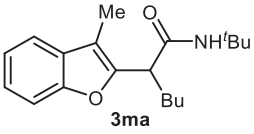
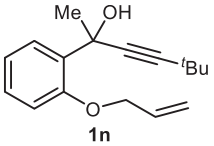
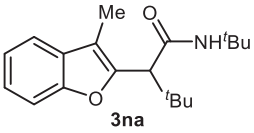
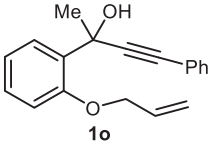
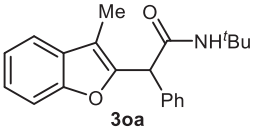
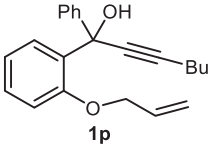
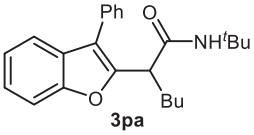
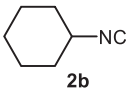
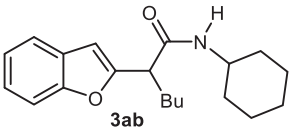
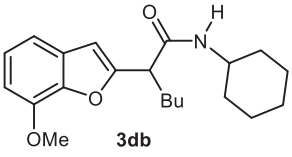
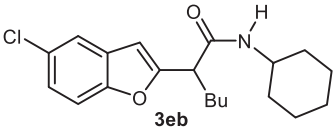
Table 2
Synthesis of 2-(benzofuran-2-yl)acetamides **3** by $Pd(PPh_3)_4$-catalyzed coupling between 1-(2-(allyloxy)phenyl)-2-yn-1-ols **1** and isocyanides **2**.[a]



Entry	1	2	3	Yield (%) of 3[b]
1	 **1a**	^{t}Bu—NC **2a**	 **3aa**	80
2	 **1b**	**2a**	 **3ba**	69
3	 **1c**	**2a**	 **3ca**	74
4	 **1d**	**2a**	 **3da**	73
5	 **1e**	**2a**	 **3ea**	65
6	 **1f**	**2a**	 **3fa**	69
7	 **1g**	**2a**	 **3ga**	65
8	 **1h**	**2a**	 **3ha**	79
9	 **1i**	**2a**	 **3ia**	76

(*continued on next page*)

Table 2 (*continued*)

Entry	1	2	3	Yield (%) of 3[b]
10	 **1j**	**2a**	 **3ja**	75
11	 **1k**	**2a**	 **3ka**	74
12	 **1l**	**2a**	 **3la**	60
13	 **1m**	**2a**	 **3ma**	73
14	 **1n**	**2a**	 **3na**	66
15	 **1o**	**2a**	 **3oa**	71
16	 **1p**	**2a**	 **3pa**	74
17	**1a**	 **2b**	 **3ab**	68
18	**1d**	**2b**	 **3db**	68
19	**1e**	**2b**	 **3eb**	66

[a] All reactions were carried out at 70 °C for 5 h in MeOH (initial concentration of **1** = 0.15 mmol per mL of MeOH) and in the presence of $Pd(PPh_3)_4$ as catalyst with a **1**:**2**:$Pd(PPh_3)_4$ molar ratio of 10:10:1.

[b] Isolated yield based on starting **1**.

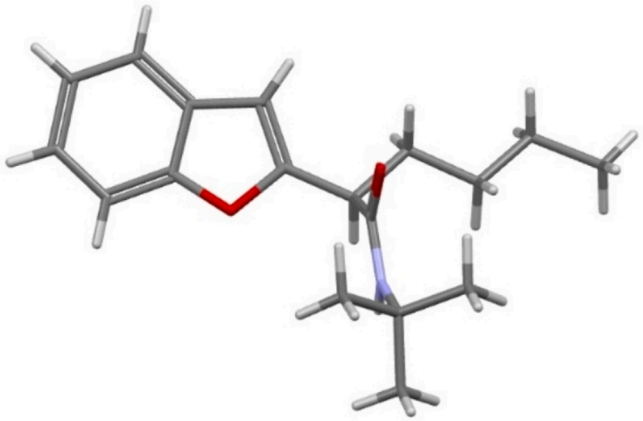


Fig. 1. X-ray molecular structure of 2-(benzofuran-2-yl)-*N*-(*tert*-butyl)hexanamide **3aa**.

the solvent; the results obtained are shown in Table 2, entries 2–19. As can be seen from Table 2, the reaction was quite general, and led to the corresponding 2-(benzofuran-2-yl)acetamides **3** in fair to good yields (60–80 %) starting from different 1-(2-(allyloxy)phenyl)-2-yn-1-ols **1a-p**, bearing either electron-withdrawing or electro-donating groups in different positions of the aromatic ring, as well as secondary or tertiary alcoholic groups and alkyl (including sterically demanding *tert*-butyl), alkenyl, or aryl substituents on the triple bond, in combination with *tert*-butyl isocyanade **2a** or cyclohexyl isocyanide **2b**. The structure of 2-(benzofuran-2-yl)-*N*-(*tert*-butyl)-2-phenylacetamide **3ha**, obtained from 1-(2-(allyloxy)phenyl)-3-phenylprop-2-yn-1-ol **1h** and **2a**, was confirmed by XRD analysis, as shown in Fig. 2 (see the Supporting Information for full XRD data). The process had some limitations, however, as no good results were obtained with butyl isocyanide or benzyl isocyanide (complicated mixtures of unidentified products were systematically observed). This is in line with the well-known tendency of less hindered isonitriles to undergo multiple insertions into the C–Pd bond, which can readily result in complex oligo- and polymerization by-reactions [1–5].

2.2. DFT study of the proposed reaction mechanism

The energetic feasibility of mechanism shown in Scheme 2 was investigated *via* quantum mechanics calculations, adopting DFT-based methodology coupled to the modeling strategy that was recently applied for Pd-containing system [27]. In the starting point of the investigation (see structure **A** in Fig. 3, corresponding to intermediate **I** of Scheme 2), Pd is coordinated to the C2 and C3 alkyne group, as evidenced by distances of 2.19 Å and 2.31 Å respectively, and to the alkoxylate moiety (Pd–O2 = 2.13 Å). In addition, the metal is tightly bounded to the η^3-allyl group (average C_{allyl}–Pd distance of 2.18 Å, see Fig. 3). An alternative binding mode of the substrate to Pd was further tested, with the metal coordinated only to η^3-allyl and to O2, resulting in + 14.3 kcal/mol with respect to **A** (see structure **A'** in Figure S5, Supporting Information).

Once the metal-substrate adduct is formed, the reaction can proceed through the attack of O2 to C2 in **TS1** (+21.3 kcal/mol above **A**, see Fig. 4), as demonstrated by by O2–C2 distance of 1.95 Å. In the relative intermediate **B** (corresponding to intermediate **II** of Scheme 2), the benzofuran ring is formed (d_{O2-C2} = 1.44 Å, see Fig. 3) in a thermodynamically favorable way, since the species lies at 18.5 kcal/mol below the reactants. With the inclusion of **2a**, which is coordinating the Pd with the C atom of isonitrile group (1.97 Å see Fig. 3), the ^{t}BuN≡C insertion takes place in **TS2**, where the formation of C3–$C_{C\equiv N\text{-}tBu}$ bond (1.84 Å) requires an energy penalty of 19.0 kcal/mol with respect to **B**. In **C** (corresponding to intermediate **III** of Scheme 2), the metal center is sandwiched by the allyl group and the nascent imidoyl group, since both the groups are binding Pd in a η^3 mode (see Fig. 3). The attack of a water molecule then allows the occurrence of **TS3** (10.4 kcal/mol with respect to **C**), in which the HO_w-$C_{C\equiv N\text{-}tBu}$ distance is 1.78 Å and one water's proton is already transferred to the N of the intermediate (see Fig. 3). The resulting **D** (corresponding to intermediate **IV** of Scheme 2) lies at –15.8 kcal/mol with respect to the reactant (see Fig. 4).

In accordance with the proposed mechanism in Scheme 2, species **D** would undergo β-H elimination with formation of the 2-(3-hydroxybenzofuran-2(3*H*)-ylidene)acetamide intermediate (**V** in Scheme 2) and an allylpalladium hydride complex (**VI** species in Scheme 2). Despite such an intermediate has been optimized (–28.9 kcal/mol with respect to the reactant, see **D-hyd** in Figure S6, Supporting Information), all the attempts to find a transition state for the **D**-to-**D-hyd** step were not fruitful. In absence of further experimental evidence, we cannot univocally rule out that this step cannot take place virtually barrierless. However, the inclusion of one methanol molecule led to formation of intermediate **D'**, at 9.1 kcal/mol from **A**, where the OH_{MeOH} is hydrogen-bonding the O1-H and the HO_w of the species. In such configuration, intermediate **D'** can evolve *via* almost barrierless intra-molecular proton-shifts in **TS4** (1.4 kcal/mol with respect to **D'**) to dehydrate the nascent product and to reach intermediate **E**, which lies at –35.7 kcal/

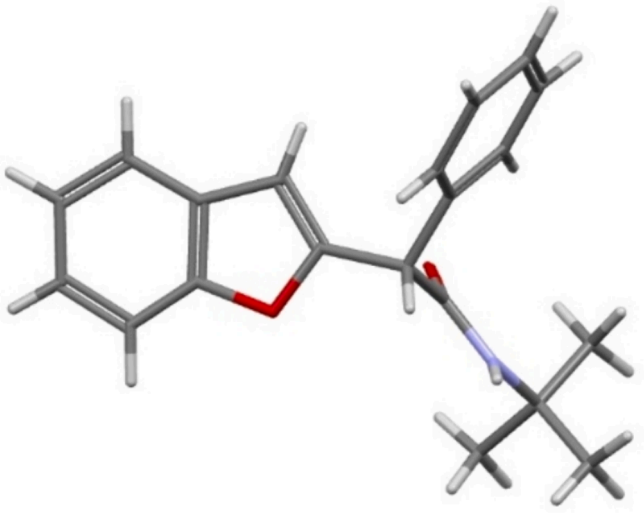
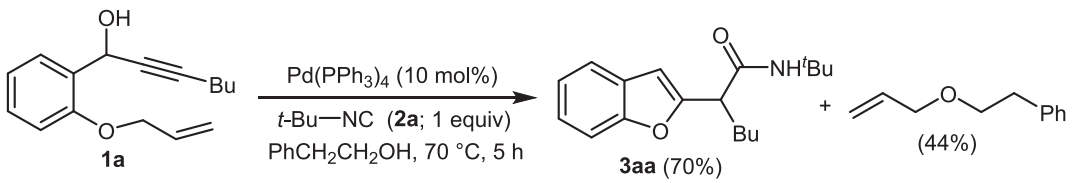


Fig. 2. X-ray molecular structure of 2-(benzofuran-2-yl)-*N*-(*tert*-butyl)-2-phenylacetamide **3 ha**.



Scheme 3. $Pd(PPh_3)_4$-catalyzed coupling between 1-(2-(allyloxy)phenyl)hept-2-yn-1-ol **1a** and *tert*-butyl isocyanide **2a** in phenethyl alcohol to give 2-(benzofuran-2-yl)-*N*-(*tert*-butyl)hexanamide **3aa** and (2-(allyloxy)ethyl)benzene.

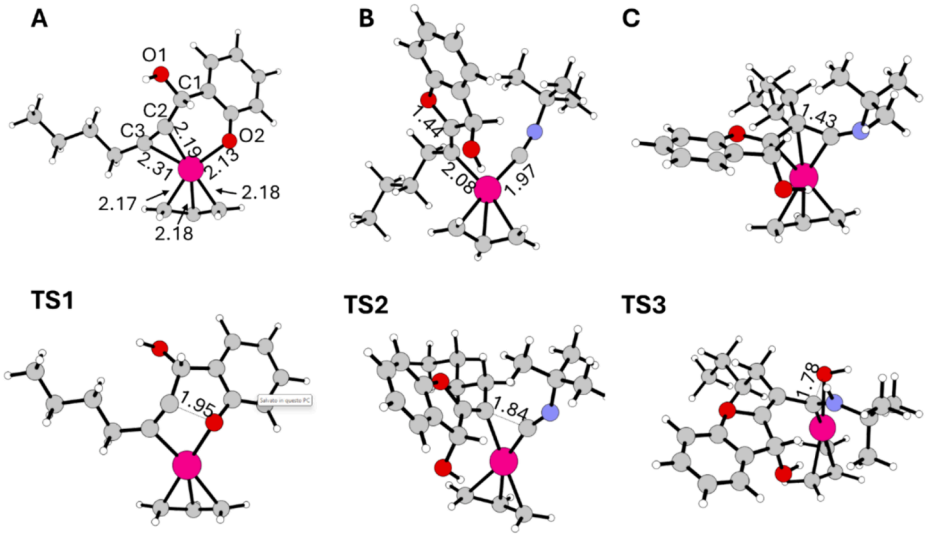


Fig. 3. Optimized geometries of intermediates **A**, **B**, **C**, on the top, and of transition states **TS1**, **TS2**, and **TS3**, at the bottom, obtained for the conversion of 1-(2-(allyloxy)phenyl)hept-2-yn-1-ol **1a** to 2-(benzofuran-2-yl)-*N*-(*tert*-butyl)hexanamide **3aa**. Distances are in Å. Pd and N are represented as pink and blue spheres while O, C and H as red, gray and white spheres, respectively.

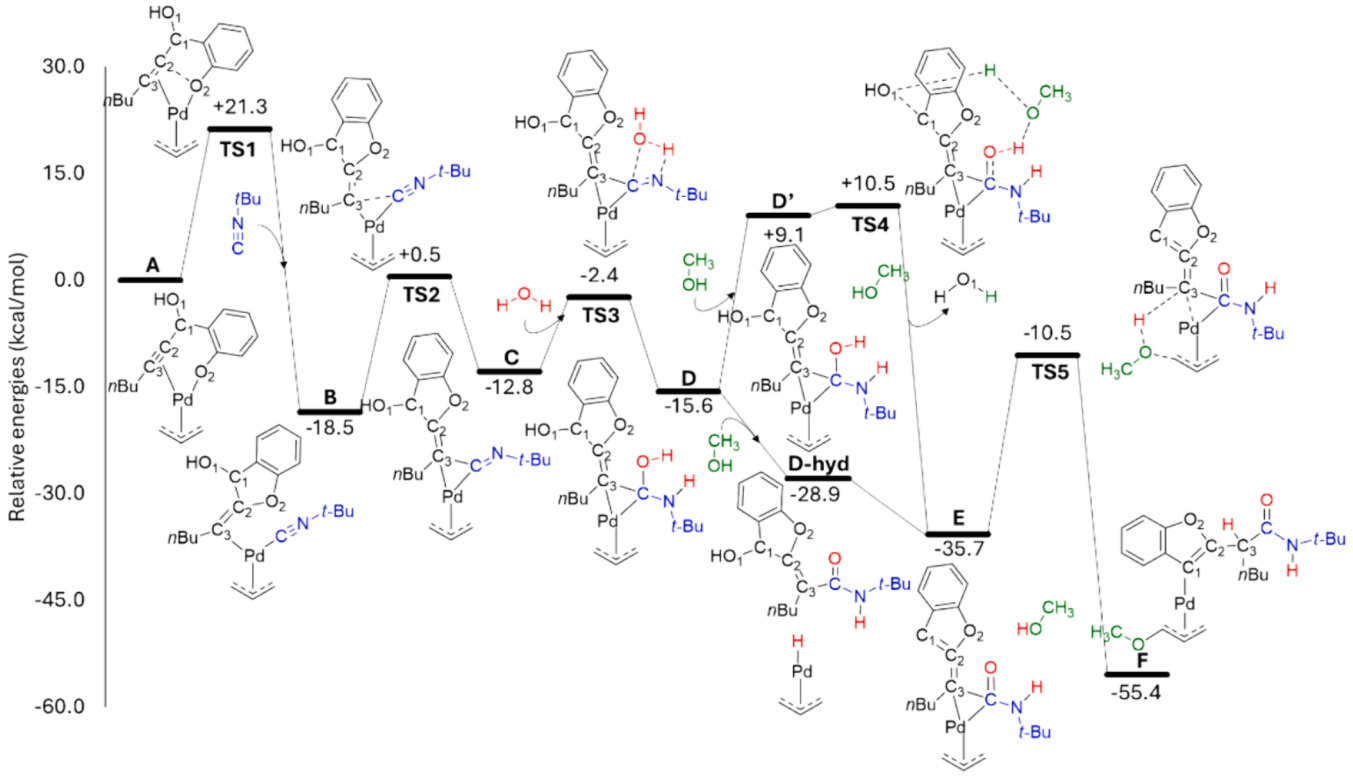


Fig. 4. Proposed reaction mechanism and related potential energy surface calculated for the conversion of 1-(2-(allyloxy)phenyl)hept-2-yn-1-ol **1a** to 2-(benzofuran-2-yl)-*N*-(*tert*-butyl)hexanamide **3aa**.

mol and that is analogous to species **VII** in Scheme 2. The scan of potential energy surfaces concerning this intramolecular proton shifts are reported in the Supporting Information file (see Figure S7). Interestingly, during the optimization of **D'** and **TS4**, Pd tends spontaneously to interact with the aromatic system of benzofuran ring (see Fig. 5). The shift of the metal generates room for the incoming MeOH molecule that can therefore perform the above-mentioned action.

Finally, in **TS5** (25.1 kcal/mol with respect to **E**, see Fig. 4), the MeOH molecule can attack the allyl group to obtain 3-methoxypropene and the final product **3aa** through intermediate **F** (see Fig. 5), with the very favorable thermodynamic of –55.4 kcal/mol. In both the transition state and the metal-product intermediate, the allyl group changes hapticity from η^3 to η^2, due to the forming C_{allyl}-O_{MeOH} bond (1.90 Å and 1.44 Å in transition state and intermediate, respectively, see Fig. 5).

Overall, the calculations showed the feasibility of the mechanism proposed in Scheme 2, with the additional suggestion of the occurrence of an intra-molecular proton shift concertedly to dehydration of the intermediate that can lead to the formation of the 2-(benzofuran-2-yl)

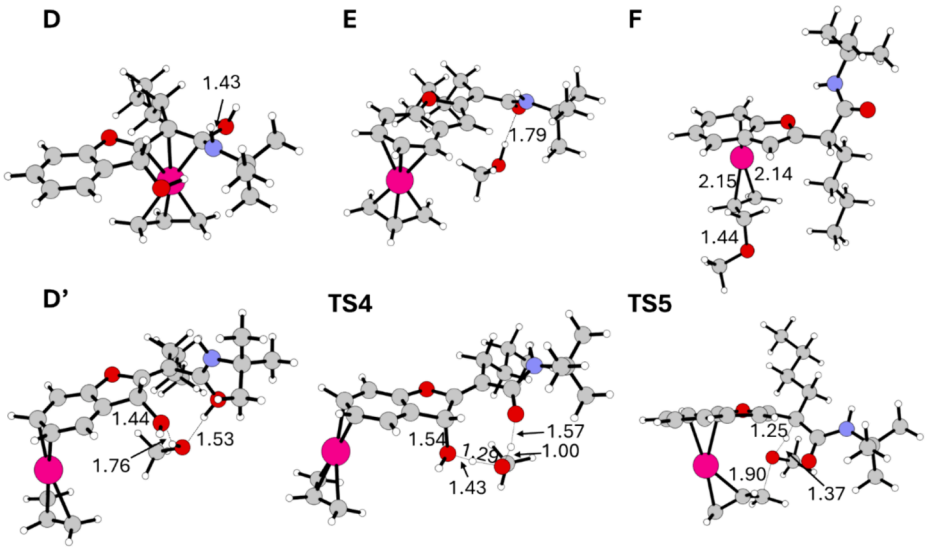


Fig. 5. Optimized geometries of intermediate **D**, **D'**, **E**, and **F**, and of transition states **TS4** and **TS5**, obtained for the conversion of 1-(2-(allyloxy)phenyl)hept-2-yn-1-ol **1a** to 2-(benzofuran-2-yl)-*N*-(*tert*-butyl)hexanamide **3aa**. Distances are in Å. Pd and N are represented as pink and blue spheres while O, C and H as red, gray and white spheres, respectively.

acetamide, mediated by the presence of one MeOH molecule (**TS4**), in addition to the alternative step through a Pd-hydride intermediate (**D-hyd**). The barriers for the intramolecular proton shifts (**TS4**) and for the alkoxy-allyl formation (**TS5**) are very close (26.1 and 25.2 kcal/mol), and it is therefore not possible to determine which step is the rate-limiting one. However, both calculated transition state energy barriers can be considered in reasonable agreement with similar systems [27].

3. Conclusions

In conclusion, we have studied the reactivity of 1-(2-(allyloxy) phenyl)-2-yn-1-ols **1** in combination with commercially available isonitriles **2** under the catalytic action of a simple commercially available catalyst, $Pd(PPh_3)_4$. We have found that the process selectively leads to high value added 2-(benzofuran-2-yl)acetamides **3** (an important class of benzofuran derivatives, which possess antifungal and anticonvulsant activities) in fair to high yields (60–80 %) over 19 examples under mild reaction conditions (70 °C for 5 h in MeOH). As corroborated by detailed DFT studies, the process takes place through a previously unreported sequence of mechanistic steps, involving oxidative addition to Pd(0) to give an (allyl)(phenoxy)palladium complex, followed by intramolecular triple bond insertion, isonitrile insertion to give (allyl)(imidoyl)palladium complex, attack by water to the imidoyl group, β-H elimination from the H-O-C-Pd(allyl) moiety, formation of a bis-allylpalladium complex with elimination of water, and nucleophilic attack by MeOH. The structures of representative products have been confirmed by X-ray diffraction analysis.

4. Experimental section

4.1. General methods

Solvent and chemicals were reagent grade and were used without further purification. All reactions were analyzed by TLC on silica gel 60 F_{254} and by GLC using 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. Melting points are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded at 25 °C on a 500 MHz Spectrometer in $CDCl_3$ as the solvent with Me_4Si as internal standard. Chemical shifts (δ) and coupling constants (*J*) are given in ppm and in Hz, respectively. IR spectra were taken with an FT-IR spectrometer. Mass spectra were obtained using a GC–MS apparatus at 70 eV ionization voltage (normal resolution) and by electrospray ionization mass spectrometry (ESI-MS) (high resolution) with a UHD accurate-mass Q-TOF spectrometer equipped with a Dual AJS ESI source working in positive mode and were recorded in the 150–1000 *m/z* range. The LC-MS experimental conditions were as follows: N_2 was employed as desolvation gas at 300 °C and a flow rate of 9 L/min. The nebulizer was set to 45 psig. The Sheat gas temperature was set at 350 °C and a flow of 12 L/min. A potential of 3.5 kV was used on the capillary for positive ion mode. The fragmentor was set to 175 V.

Preparation of Substrates. 3-(2-(Methylthio)phenyl)prop-2-yn-1-ols **1a-p** were prepared as we already reported [24]. *tert*-Butyl isocyanide **2a**, cyclohexyl isocyanide **2b**, butyl isocyanide, and benzyl isocyanide were commercially available (Merck) and were used as received.

General procedure for the synthesis of 2-(benzofuran-2-yl) acetamides 3aa-3pa and 3ab-3eb by catalytic coupling of 1-(2-(allyloxy)phenyl)-2-yn-1-ols 1 and isonitriles 2 (Table 2).

In a typical experiment, $Pd(PPh_3)_4$ (44.0 mg, 0.038 mmol) and isonitriles **2** (0.38 mmol; **2a**, 31.6 mg; **2b**, 41.5 mg) were added under nitrogen to a solution of substrate **1** (0.38 mmol; **1a**, 93.5 mg; **1b**, 105.0 mg; **1c**, 105.3 mg; **1d**, 105.1 mg; **1e**, 106.2 mg; **1f**, 93.7 mg; **1g**, 102.5 mg; **1h**, 101.2 mg; **1i**, 112.6 mg; **1j**, 112.0 mg; **1k**, 112.2 mg; **1l**, 114.2 mg; **1m**, 98.3 mg; **1n**, 99.0 mg; **1o**; 106.5 mg, **1p**, 122.2 mg) in MeOH (2.5 mL) in a Schlenk flask. The resulting mixture was stirred under nitrogen at 70 °C for 5 h. Solvent was evaporated, and products **3** were purified by column chromatography on silica gel using as eluent hexane-AcOEt from 100:0 to 95:5 to give pure products **3**. All products **3**, with the exception of **3aa** [23], were new compounds.

2-(Benzofuran-2-yl)-N-(tert-butyl)hexanamide (**3aa**). Yield: 88.2 mg, starting from 93.5 mg of 1-(2-(allyloxy)phenyl)hept-2-yn-1-ol **1a** (80 %; Table 2, entry 1). Yellow solid, mp = 79–80 °C. IR (KBr): ν = 3318 (m, br), 1651 (s), 1551 (m), 1450 (m), 1389 (w), 1366 (w), 1250 (m), 1227 (w), 748 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.55–7.49 (m, 1H), 7.46–7.41 (m, 1H), 7.27–7.17 (m, 2H), 6.58 (s, 1H), 5.59 (s, br, 1H), 3.52–3.44 (m, 1H), 2.15–2.02 (m, 1H), 1.98–1.86 (m, 1H), 1.40–1.22 (m, 13H), 0.92–0.83 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.1, 156.7, 154.7, 128.5, 123.9, 122.8, 120.8, 111.0, 103.7, 51.4, 48.5, 30.9, 29.7, 28.7, 22.5, 13.9; GC–MS: *m/z* = 287 (M^+, 5), 188 (61), 131 (100), 108 (8); HRMS-ESI (*m/z*): [(M + H)$^+$] calcd for $(C_{18}H_{26}NO_2)^+$:

288.1958; found, 288.1989. The spectroscopic data agreed with those reported [23].

N-(tert-Butyl)-2-(6-methoxybenzofuran-2-yl)hexanamide (**3ba**). Yield: 84.2 mg, starting from 105.0 mg of 1-(2-(allyloxy)-4-methoxyphenyl) hept-2-yn-1-ol **1b** (69 %; Table 2, entry 2). Yellow solid, mp = 89–91 °C. IR (KBr): ν = 3325 (m, br), 1651 (s), 1489 (m), 1366 (w), 1296 (w), 1150 (m), 1111 (w), 1026 (w), 826 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.37 (dist d, J = 8.5, 1H), 7.00 (d, J = 2.0, 1H), 6.85 (dd, J = 8.5, 2.0, 1H), 6.49 (s, 1H), 5.54 (s, br, 1H), 3.85 (s, 3H), 3.45 (t, J = 7.6, 1H), 2.12–2.01 (m, 1H), 1.96–1.85 (m, 1H), 1.40–1.23 (m, 13H), 0.89 (t, J = 6.9, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.8, 157.2, 155.2, 121.2, 120.8, 120.3, 111.2, 103.0, 95.5, 55.2, 50.3, 48.1, 30.3, 29.2, 28.1, 22.0, 13.4; GC–MS: m/z = 317 (M^+, 29), 218 (91), 217 (89), 175 (9), 161 (100), 137 (14); HRMS-ESI (m/z): [(M + H)$^+$] calcd for $(C_{19}H_{28}NO_3)^+$: 318.2064; found, 318.2080.

N-(tert-Butyl)-2-(5-methoxybenzofuran-2-yl)hexanamide (**3ca**). Yield: 90.5 mg, starting from 105.3 mg of 1-(2-(allyloxy)-5-methoxyphenyl) hept-2-yn-1-ol **1c** (74 %; Table 2, entry 3). Yellow solid, mp = 75–77 °C. IR (KBr): ν = 3318 (m, br), 1651 (s), 1551 (m), 1474 (m), 1450 (m), 1366 (w), 1204 (m), 1034 (m), 802 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.35 (d, J = 8.9, 1H), 7.01 (d, J = 2.5, 1H), 6.87 (dist dd, J = 8.9, 2.5, 1H), 6.53 (s, 1H), 5.59 (s, br, 1H), 3.85 (s, 3H), 3.49 (t, J = 7.6, 1H), 2.16–2.06 (m, 1H), 1.99–1.88 (m, 1H), 1.42–1.29 (m, 13H), 0.95–0.87 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.1, 157.6, 156.0, 149.7, 129.1, 112.4, 111.4, 103.9, 103.5, 55.9, 51.4, 48.6, 30.9, 29.7, 28.7, 22.5, 13.9; GC–MS: m/z = 317 (M^+, 15), 218 (100), 175 (22), 161 (25), 137 (18); HRMS-ESI (m/z): [(M+H)$^+$] calcd for $(C_{19}H_{28}NO_3)^+$: 318.2064; found, 318.2084.

N-(tert-Butyl)-2-(7-methoxybenzofuran-2-yl)hexanamide (**3da**). Yield: 88.5 mg, starting from 105.1 mg of 1-(2-(allyloxy)-3-methoxyphenyl) hept-2-yn-1-ol **1d** (73 %; Table 2, entry 4). Yellow solid, mp = 75–77 °C. IR (KBr): ν = 3317 (m, br), 1652 (s), 1540 (m), 1492 (m), 1456 (m), 1362 (w), 1270 (m), 1220 (m), 1097 (m), 772 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.15–7.10 (m, 2H), 6.80–6.75 (m, 1H), 6.58 (s, 1H), 5.64 (s, br, 1H), 4.00 (s, 3H), 3.51 (t, J = 7.6, 1H), 2.15–2.05 (m, 1H), 2.00–1.87 (m, 1H), 1.36–1.29 (m, 13H), 0.88 (t, J = 6.9, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.1, 157.6, 145.2, 130.2, 123.5, 113.3, 106.2, 103.8, 56.1, 51.4, 48.4, 31.3, 29.8, 28.7, 22.5, 13.9; GC–MS: m/z = 317 (M^+, 10), 218 (80), 175 (24), 161 (100), 138 (17); HRMS-ESI (m/z): [(M + H)$^+$] calcd for $(C_{19}H_{28}NO_3)^+$: 318.2064; found, 318.2080.

N-(tert-Butyl)-2-(5-chlorobenzofuran-2-yl)hexanamide (**3ea**). Yield: 80.2 mg, starting from 106.2 mg of 1-(2-(allyloxy)-5-chlorophenyl)hept-2-yn-1-ol **1e** (65 %; Table 2, entry 5). Yellow solid, mp = 152–153 °C. IR (KBr): ν = 3317 (m, br), 1653 (s), 1545 (m), 1448 (m), 1364 (w), 1258 (m), 1225 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.48 (d, J = 1.8, 1H), 7.34 (dist d, J = 8.6, 1H), 7.20 (dist dd, J = 8.6, 1.8, 1H), 6.53 (s, 1H), 5.53 (s, br, 1H), 3.47 (t, J = 7.5, 1H), 2.14–2.02 (m, 1H), 1.96–1.86 (m, 1H), 1.45–1.20 (m, 13H), 0.89 (t, J = 6.8, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.7, 158.5, 153.1, 129.9, 128.4, 124.0, 120.4, 111.9, 103.2, 51.5, 48.5, 30.8, 29.7, 28.7, 22.5, 13.9; GC–MS: m/z = 321 (M^+, 2), 265 (3), 224 (24), 222 (72), 179 (8), 167 (23), 165 (70), 115 (7), 81 (30), 57 (100); HRMS-ESI (m/z): [(M + H)$^+$] calcd for $(C_{18}H_{25}ClNO_2)^+$: 322.1568; found, 322.1575.

2-(Benzofuran-2-yl)-N-(tert-butyl)-3,3-dimethylbutamide (**3fa**). Yield: 76.5 mg, starting from 93.7 mg of 1-(2-(allyloxy)phenyl)-4,4-dimethylpent-2-yn-1-ol **1f** (69 %; Table 2, entry 6). Yellow solid, mp = 80–82 °C. IR (KBr): ν = 3324 (m, br), 1659 (s), 1548 (m), 1454 (m), 1365 (w), 1254 (m), 1225 (w), 751 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.56–7.52 (m, 1H), 7.47–7.42 (m, 1H), 7.27–1.17 (m, 2H), 6.71 (s, 1H), 5.74 (s, br, 1H), 3.31 (s, 1H), 1.33 (s, 9H), 1.11 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.1, 155.4, 154.5, 128.6, 123.6, 122.8, 120.8, 110.8, 105.5, 58.7, 54.8, 51.4, 28.7, 28.5; GC–MS: m/z = 287 (M^+, 6), 231 (29), 187 (54), 188 (43), 173 (25), 158 (31), 145 (25), 131 (33), 57 (100); HRMS-ESI (m/z): [(M + H)$^+$] calcd for $(C_{18}H_{26}NO_2)^+$: 288.1958; found, 288.1971.

2-(Benzofuran-2-yl)-N-(tert-butyl)-2-(cyclohex-1-en-1-yl)acetamide (**3ga**). Yield: 77.0 mg, starting from 102.5 mg of 1-(2-(allyloxy)phenyl)-3-(cyclohex-1-en-1-yl)prop-2-yn-1-ol **1g** (65 %; Table 2, entry 7). Colorless solid, mp = 103–106 °C. IR (KBr): ν = 3318 (m, br), 1652 (s), 1547 (m), 1455 (m), 1364 (w), 1254 (m), 1224 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.54–7.50 (m, 1H), 7.46–7.42 (m, 1H), 7.27–7.22 (m, 1H), 7.22–7.18 (m, 1H), 6.63 (s, 1H), 5.79 (s, br, 1H), 5.65 (s, 1H), 4.22 (s, 1H), 2.11–2.02 (m, 4H), 1.69–1.62 (m, 2H), 1.62–1.55 (m, 2H), 1.40–1.33 (m, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.2, 155.2, 154.8, 134.8, 128.4, 126.4, 123.8, 122.7, 120.8, 111.0, 105.0, 56.5, 51.4, 28.6, 27.7, 25.4, 22.9, 22.0; GC–MS: m/z = 311 (M^+, 5), 212 (100), 211 (52), 183 (13), 144 (18), 131 (51), 115 (10), 57 (54); HRMS-ESI (m/z): [(M + H)$^+$] calcd for $(C_{20}H_{26}NO_2)^+$: 312.1958; found, 312.1956.

2-(Benzofuran-2-yl)-N-(tert-butyl)-2-phenylacetamide (**3ha**). Yield: 93.2 mg, starting from 101.2 mg of 1-(2-(allyloxy)phenyl)-3-phenylprop-2-yn-1-ol **1h** (79 %; Table 2, entry 8). Yellow solid, mp = 175–176 °C. IR (KBr): ν = 3302 (m), 1659 (s), 1543 (m), 1358 (w), 1319 (m), 1234 (w), 1065 (m), 988 (m), 764 (m), 725 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.55–7.46 (m, 1H), 7.46–7.28 (m, 6H), 7.28–7.25 (m, 2H), 6.58 (s, 1H), 5.66 (s, br, 1H), 4.95 (s, 1H), 1.33 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.3, 155.6, 155.0, 136.9, 128.9, 128.5, 128.3, 127.8, 124.0, 122.8, 120.9, 111.1, 105.5, 54.5, 51.7, 28.6; GC–MS: m/z = 307 (M^+, 0.4), 208 (75), 207 (100), 178 (24); HRMS-ESI (m/z): [(M + H)$^+$] calcd for $(C_{20}H_{22}NO_2)^+$: 308.1645; found, 308.1669.

N-(tert-Butyl)-2-(5-methoxybenzofuran-2-yl)-2-phenylacetamide (**3ia**). Yield: 98.5 mg, starting from 112.6 mg of 1-(2-(allyloxy)-5-methoxyphenyl)-3-phenylprop-2-yn-1-ol **1i** (76 %; Table 2, entry 9). Yellow solid, mp = 165–167 °C. IR (KBr): ν = 3322 (m, br), 1657 (s), 1621 (w), 1598 (m), 1493 (m), 1454 (w), 1365 (w), 1270 (m), 1223 (m), 1096 (m), 977 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.39–7.34 (m, 4H), 7.33–7.27 (m, 2H), 7.00 (d, J = 2.2, 1H), 6.87–6.83 (m, 1H), 6.52 (s, 1H), 5.61 (s, br, 1H), 4.91 (s, 1H), 3.82 (s, 3H), 1.34 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.2, 156.4, 156.0, 150.0, 136.9, 128.9, 128.5, 127.8, 112.7, 111.6, 111.5, 105.7, 103.5, 55.9, 54.6, 29.6, 28.6; GC–MS: m/z = 337 (M^+, 2), 237 (100), 222 (4), 194 (13), 165 (13); HRMS-ESI (m/z): [(M + H)$^+$] calcd for $(C_{21}H_{24}NO_3)^+$: 338.1751; found, 338.1760.

N-(tert-Butyl)-2-(6-methoxybenzofuran-2-yl)-2-phenylacetamide (**3ja**). Yield: 96.2 mg, starting from 112.0 mg of 1-(2-(allyloxy)-6-methoxyphenyl)-3-phenylprop-2-yn-1-ol **1j** (75 %; Table 2, entry 10). Yellow solid, mp = 165–167 °C. IR (KBr): ν = 3290 (m, br), 1648 (s), 1556 (m), 1493 (m), 1453 (w), 1361 (w), 1229 (w), 1150 (m), 1107 (w), 1029 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.42–7.26 (m, 6H), 6.97 (d, J = 0.8, 1H), 6.84 (dd, J = 8.5, 2.0, 1H), 6.49 (s, 1H), 5.64 (s, br, 1H), 4.91 (s, 1H), 3.82 (s, 3H), 1.33 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.5, 157.8, 156.0, 154.7, 137.1, 128.9, 128.5, 127.7, 121.6, 121.0, 111.8, 105.3, 96.0, 55.7, 54.5, 29.6, 28.6; GC–MS: m/z = 337 (M^+, 4), 237 (100), 222 (9), 194 (12), 165 (14); HRMS-ESI (m/z): [(M + H)$^+$] calcd for $(C_{21}H_{24}NO_3)^+$: 338.1751; found, 338.1758.

N-(tert-Butyl)-2-(7-methoxybenzofuran-2-yl)-2-phenylacetamide (**3ka**). Yield: 95.0 mg, starting from 112.2 mg of 1-(2-(allyloxy)-3-methoxyphenyl)-3-phenylprop-2-yn-1-ol **1k** (74 %; Table 2, entry 11). Yellow solid, mp = 158–160 °C. IR (KBr): ν = 3323 (m, br), 1656 (s), 1598 (w), 1492 (m), 1437 (w), 1364 (w), 1222 (m), 1177 (w), 1096 (m), 730 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.39–7.32 (m, 4H), 7.32–7.28 (m, 1H), 7.15–7.08 (m, 2H), 6.77 (dist dd, J = 6.8, 1.6, 1H), 6.57 (s, 1H), 5.64 (s, br, 1H), 4.96 (s, 1H), 3.97 (s, 3H), 1.33 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.3, 156.0, 145.2, 144.2, 137.0, 130.1, 128.9, 128.5, 127.7, 123.5, 113.4, 106.5, 105.8, 56.0, 54.4, 51.7, 28.6; GC–MS: m/z = 337 (M^+, 2), 237 (100), 194 (13), 165 (13); HRMS-ESI (m/z): [(M + H)$^+$] calcd for $(C_{21}H_{24}NO_3)^+$: 338.1751; found, 338.1769.

N-(tert-Butyl)-2-(5-chlorobenzofuran-2-yl)-2-phenylacetamide (**3la**). Yield: 78.8 mg, starting from 114.2 mg of 1-(2-(allyloxy)-5-chlorophenyl)-3-phenylprop-2-yn-1-ol **1l** (60 %; Table 2, entry 12). Yellow solid, mp = 140–141 °C. IR (KBr): ν = 3325 (m, br), 1651 (s), 1543 (w), 1450 (m), 1389 (w), 1366 (m), 1258 (m), 1219 (w), 756 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.48–7.44 (m, 1H), 7.40–7.29 (m, 6H), 7.19 (dist dd, J = 8.6, 2.0, 1H), 6.53 (s, 1H), 5.55 (s, br, 1H), 4.91 (s, 1H),

1.33 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.0, 157.6, 153.4, 136.5, 129.7, 129.0, 128.5, 128.4, 128.0, 124.2, 120.5, 112.1, 105.1, 54.4, 51.8, 28.6; GC–MS: *m/z* = 341 (M^+, 0.5), 244 (25), 243 (43), 242 (75), 241 (100), 207 (10), 205 (12), 178 (12), 57 (56); HRMS-ESI (*m/z*): [(M + H)$^+$] calcd for $(C_{20}H_{21}ClNO_2)^+$: 342.1255; found, 342.1280.

N-(tert-Butyl)-2-(3-methylbenzofuran-2-yl)hexanamide (**3ma**). Yield: 84.0 mg, starting from 98.3 mg of 2-(2-(allyloxy)phenyl)oct-3-yn-2-ol **1m** (73 %; Table 2, entry 13). Yellow solid, mp = 72–74 °C. IR (KBr): ν = 3384 (m, br), 1646 (s), 1554 (m), 1477 (m), 1365 (w), 1260 (w), 1050 (w), 744 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.48 (d, *J* = 7.1, 1H), 7.43 (d, *J* = 7.5, 1H), 7.30–7.20 (m, 2H), 5.67 (s, br, 1H), 3.60 (dist dd, *J* = 9.7, 5.7, 1H), 2.21 (s, 3H), 2.17–2.06 (m, 1H), 2.01–1.90 (m, 1H), 1.44–1.10 (m, 13H), 0.85 (t, *J* = 7.1, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.5, 154.1, 150.8, 130.1, 124.0, 122.5, 119.2, 112.6, 110.9, 51.3, 46.7, 31.0, 29.8, 28.7, 22.4, 13.9, 8.0; GC–MS: *m/z* = 301 (M^+, 5), 202 (48), 201 (27), 158 (5), 145 (100), 115 (8), 57 (13); HRMS-ESI (*m/z*): [(M + H)$^+$] calcd for $(C_{19}H_{28}NO_2)^+$: 302.2115; found, 302.2114.

N-(tert-Butyl)-3,3-dimethyl-2-(3-methylbenzofuran-2-yl)butanamide (**3na**). Yield: 76.0 mg, starting from 99.0 mg of 2-(2-(allyloxy)phenyl)-5,5-dimethylhex-3-yn-2-ol **1n** (66 %; Table 2, entry 14). Yellow solid, mp = 69–71 °C. IR (KBr): ν = 3324 (m, br), 1651 (m), 1584 (m), 1488 (m), 1365 (w), 1241 (s), 1051 (w), 903 (w) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.52–7.46 (m, 1H), 7.46–7.40 (m, 1H), 7.31–7.21 (m, 3H), 6.28 (s, 1H), 3.47 (s, 1H), 2.20 (s, 3H), 1.32 (s, 9H), 1.11 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.9, 153.8, 150.4, 129.7, 123.9, 122.6, 119.3, 113.6, 110.6, 56.7, 51.2, 35.7, 28.9, 28.7, 8.3; GC–MS: *m/z* = 301 (M^+, 15), 245 (42), 201 (100), 189 (56), 172 (27), 145 (55), 115 (12); HRMS-ESI (*m/z*): [(M + H)$^+$] calcd for $(C_{19}H_{28}NO_2)^+$: 302.2115; found, 302.2127.

N-(tert-Butyl)-2-(3-methylbenzofuran-2-yl)-2-phenylacetamide (**3oa**). Yield: 87.5 mg, starting from 106.5 mg of 2-(2-(allyloxy)phenyl)-4-phenylbut-3-yn-2-ol **1o** (71 %; Table 2, entry 15). Yellow solid, mp = 158–160 °C. IR (KBr): ν = 3273 (m, br), 1651 (s), 1562 (m), 1478 (m), 1455 (w), 1249 (m), 1223 (w), 1088 (w), 743 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.54–7.38 (m, 2H), 7.38–7.18 (m, 7H), 5.88 (s, br, 1H), 5.06 (s, 1H), 2.24 (s, 3H), 1.33 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.6, 154.1, 149.6, 137.3, 129.9, 128.8, 128.3, 127.5, 124.1, 122.5, 119.4, 113.3, 111.0, 52.4, 51.6, 28.6, 8.1; GC–MS: *m/z* = 321 (M^+, 0.6), 222 (70), 221 (100), 207 (13), 202 (8), 178 (8), 115 (6); HRMS-ESI (*m/z*): [(M + H)$^+$] calcd for $(C_{21}H_{24}NO_2)^+$: 322.1802; found, 322.1810.

N-(tert-Butyl)-2-(3-phenylbenzofuran-2-yl)hexanamide (**3pa**). Yield: 102.3 mg, starting from 122.2 mg of 1-(2-(allyloxy)phenyl)-1-phenylhept-2-yn-1-ol **1p** (74 %; Table 2, entry 16). Yellow solid, mp = 90–93 °C. IR (KBr): ν = 3341 (m, br), 1666 (s), 1520 (m), 1451 (m), 1389 (w), 1367 (m), 1219 (m), 964 (w), 748 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.63–7.50 (m, 6H), 7.46–7.40 (m, 1H), 7.38–7.34 (m, 1H), 7.32–7.27 (m, 1H), 5.63 (s, br, 1H), 3.74 (dd, *J* = 9.5, 6.1, 1H), 2.21–2.01 (m, 2H), 1.36–1.23 (m, 13H), 0.85 (t, *J* = 7.1, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.3, 154.2, 151.4, 131.7, 129.2, 129.0, 128.5, 127.7, 124.4, 123.0, 120.0, 119.7, 111.3, 51.3, 46.7, 30.7, 29.7, 28.7, 22.4, 13.8; GC–MS: *m/z* = 363 (M^+, 2), 264 (100), 263 (38), 207 (81), 179 (17); HRMS-ESI (*m/z*): [(M + H)$^+$] calcd for $(C_{24}H_{30}NO_2)^+$: 364.2271; found, 364.2294.

2-(Benzofuran-2-yl)-N-cyclohexylhexanamide (**3ab**). Yield: 81.4 mg, starting from 93.0 mg of 1-(2-(allyloxy)phenyl)hept-2-yn-1-ol **1a** (68 %; Table 2, entry 17). White solid, mp 100–102 °C. IR (KBr): ν = 3292 (m, br), 1646 (s), 1558 (w), 1540 (m), 1521 (m), 1456 (m), 1251 (w), 752 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.53 (dist d, *J* = 7.2, 1H), 7.44 (dist d, *J* = 7.8, 1H), 7.29–7.18 (m, 2H), 6.59 (s, 1H), 5.60 (s, br, 1H), 3.82–3.68 (m, 1H), 3.57 (t, *J* = 7.4, 1H), 2.19–2.05 (m, 1H), 2.01–1.90 (m, 1H), 1.90–1.79 (m, 1H), 1.71–1.50 (m, 5H), 1.42–1.23 (m, 6H), 1.19–1.00 (m, 2H), 0.98 (t, *J* = 0.9, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.9, 156.5, 154.7, 128.4, 123.9, 122.8, 120.8, 111.0, 104.1, 48.4, 47.9, 32.9, 30.8, 29.7, 25.5, 24.7, 22.5, 13.9; GC–MS: *m/z* = 313 (M^+, 5), 257 (100), 188 (26), 187 (19), 173 (36), 158 (46), 132 (48); HRMS-ESI (*m/z*): [(M+H)$^+$] calcd for $(C_{20}H_{28}NO_2)^+$: 314.2115; found, 314.2112.

N-Cyclohexyl-2-(7-methoxybenzofuran-2-yl)hexanamide (**3db**). Yield: 89.1 mg, starting 105.0 mg of 1-(2-(allyloxy)-3-methoxyphenyl)hept-2-yn-1-ol **1d** (68 %; Table 2, entry 18). White solid, 95–98 °C. IR (KBr): ν = 3309 (m, br), 1653 (s), 1540 (m), 1490 (m), 1457 (w), 1436 (w), 1362 (w), 1270 (w), 1221 (m), 1097 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.28–7.25 (m, 1H), 7.17–7.11 (m, 1H), 6.78 (dist dd, *J* = 6.4, 2.0, 1H), 6.59 (s, 1H), 5.64 (s, br, 1H), 4.00 (s, 3H), 3.81–3.69 (m, 1H), 3.58 (t, *J* = 7.6, 1H), 2.20–2.10 (m, 1H), 2.01–1.91 (m, 1H), 1.91–1.81 (m, 2H), 1.72–1.51 (m, 5H), 1.42–1.21 (m, 5H), 1.21–1.01 (m, 2H), 0.95–0.81 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.8, 156.8, 145.1, 130.3, 129.6, 123.5, 113.2, 106.2, 104.1, 56.1, 48.4, 47.9, 32.9, 31.2, 29.8, 25.5, 24.7, 22.5, 13.9; GC–MS: *m/z* = 343 (M^+, 13), 218 (100), 175 (40), 161 (88), 138 (30); HRMS-ESI (*m/z*): [(M+H)$^+$] calcd for $(C_{21}H_{30}NO_3)^+$: 344.2220; found, 344.2217.

2-(5-Chlorobenzofuran-2-yl)-N-cyclohexylhexanamide (**3eb**). Yield: 87.5 mg, starting from 106.1 mg of 1-(2-(allyloxy)-5-chlorophenyl)hept-2-yn-1-ol **1e** (66 %; Table 2, entry 19). White solid, mp 112–113 °C. IR (KBr): ν = 3292 (m, br), 1646 (s), 1558 (m), 1540 (w), 1447 (m), 1259 (w), 800 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.49 (d, *J* = 1.2, 1H), 7.35 (dist d, *J* = 8.6, 1H), 7.21 (dist dd, *J* = 10.7, 1.2, 1H), 6.55 (s, 1H), 5.55 (s, br, 1H), 3.82–3.70 (m, 1H), 3.54 (t, *J* = 7.9, 1H), 2.15–2.05 (m, 1H), 1.99–1.81 (m, 2H), 1.70–1.51 (m, 5H), 1.41–1.21 (m, 6H), 1.19–1.01 (m, 2H), 0.89 (t, *J* = 6.9, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.5, 158.2, 153.1, 128.8, 128.5, 124.1, 120.4, 112.0, 103.4, 48.4, 47.9, 32.9, 30.8, 29.7, 25.5, 24.7, 22.6, 13.9; GC–MS: *m/z* = 349 [(M+2)$^+$, 1], 347 (2), 291 (7), 224 (16), 222 (52), 187 (10), 167 (22), 165 (61), 83 (100); HRMS-ESI (*m/z*): [(M+H)$^+$] calcd for $(C_{20}H_{27}ClNO_2)^+$: 348.1725; found, 348.1713.

Synthesis of 2-(benzofuran-2-yl)-*N*-(*tert*-butyl)hexanamide 3aa in larger scale.

$Pd(PPh_3)_4$ (220.0 mg, 0.19 mmol) and *tert*-butyl isocyanide **2a** (160.0 mg, 1.92 mmol) were added under nitrogen to a solution of 1-(2-(allyloxy)phenyl)hept-2-yn-1-ol **1a** (470.0 mg, 1.92 mmol) in MeOH (12.8 mL) in a Schlenk flask. The resulting mixture was stirred under nitrogen at 70 °C for 5 h. Solvent was evaporated, and the crude product was purified by column chromatography on silica gel using as eluent hexane-AcOEt from 100:0 to 95:5, to give pure 2-(benzofuran-2-yl)-*N*-(*tert*-butyl)hexanamide **3aa** as a colorless solid (yield: 432.0 mg, 78 %).

Reaction between 1-(2-(allyloxy)phenyl)hept-2-yn-1-ol 1a and *tert*-butyl isocyanide 2a in phenethyl alcohol (Scheme 3).

$Pd(PPh_3)_4$ (44.0 mg, 0.038 mmol) and *tert*-butyl isocyanide **2a** (31.8 mg, 0.38 mmol) were added under nitrogen to a solution of 1-(2-(allyloxy)phenyl)hept-2-yn-1-ol **1a** (93.5 mg, 0.38 mmol) in phenethyl alcohol (2.5 mL) in a Schlenk flask. The resulting mixture was stirred under nitrogen at 70 °C for 5 h. Solvent was evaporated, and products (2-(allyloxy)ethyl)benzene (colorless oil; yield: 27.5 mg, 44 %) and **3aa** (colorless solid; yield: 77.2 mg, 70 %) were separated in this order by column chromatography on silica gel using as eluent hexane-AcOEt from 100:0 to 95:5.

(2-(Allyloxy)ethyl)benzene. Yield: 27.5 mg, starting from 93.5 mg of 1-(2-(allyloxy)phenyl)hept-2-yn-1-ol **1a** (44 %; eq. 1). Colorless oil. IR (film): ν = 2857 (m), 1507 (m), 1455 (m), 1101 (s), 1031 (w), 992 (w), 923 (m), 749 (m), 699 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.32–7.25 (m, 2H), 7.25–7.16 (m, 3H), 5.96–5.85 (m, 1H), 5.25 (d, *J* = 17.2, 1H), 5.16 (dist d, *J* = 10.4, 1H), 4.00 (d, *J* = 5.5, 2H), 3.65 (t, *J* = 7.3, 2H), 2.29 (t, *J* = 7.3, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 138.9, 134.8, 128.9, 128.3, 126.2, 116.9, 71.9, 71.2, 36.4; GC–MS: *m/z* = 162 (M^+, 0.6), 105 (67), 91 (100), 77 (15), 71 (13), 65 (28). The spectroscopic data were in good agreement with those reported [28].

4.2. Computational details

All calculations were performed using Gaussian16 software package [29], selecting the B3LYP functional [30,31] and including D3

dispersion [32]. In agreement with the procedure reported recently, [27,33–35] H, C, N, O atoms were treated *via* 6-31G(d,p) basis set, while the SDD pseudopotential was adopted for Pd [36]. Geometry optimizations were carried out adopting the SMD implicit solvation method [37] in methanol environment (ε = 32.613), in agreement with the experimental conditions described above. At the same level of theory, frequency calculations were performed to confirm the nature of minima or transition states. Final energies concern Gibbs free energy corrections at 298 K and the electronic energy, obtained by the inclusion of dispersions and solvent effects.

CRediT authorship contribution statement

Raffaella Mancuso: Validation, Methodology, Investigation, Data curation. **Patrizio Russo:** Validation, Methodology, Investigation, Data curation. **Mario Prejanò:** Writing – original draft, Validation, Methodology, Investigation. **Antonio Plaumbo Piccionello:** Validation, Methodology. **Corrado Cuocci:** Methodology, Investigation. **Tiziana Marino:** Writing – original draft, Validation, Methodology, Investigation. **Bartolo Gabriele:** Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Methodology, Funding acquisition, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplementary material

Supplementary material to this article can be found online at https://doi.org/10.1016/j.jcat.2024.115659.

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