

## Article

# An Oxidant-Free and Mild Strategy for Quinazolin-4(3*H*)-One Synthesis via CuAAC/Ring Cleavage Reaction

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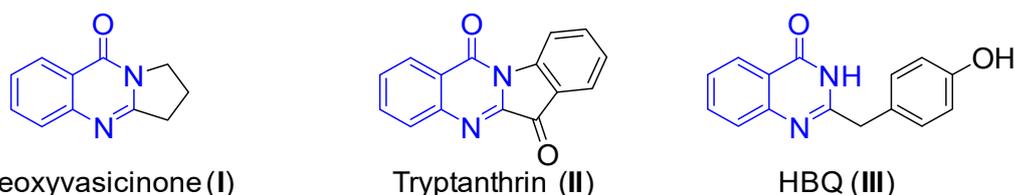
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**Abstract:** An oxidant-free and highly efficient synthesis of phenolic quinazolin-4(3*H*)-ones was achieved by simply stirring a mixture of 2-aminobenzamides, sulfonyl azides, and terminal alkynes. The intermediate *N*-sulfonylketenimine underwent two nucleophilic additions and the sulfonyl group eliminated through the power of aromatization. The natural product 2-(4-hydroxybenzyl)quinazolin-4(3*H*)-one can be synthesized on a large scale under mild conditions with this method.

**Keywords:** CuAAC/ring cleavage reaction; nucleophilic addition; natural product; quinazolin-4(3*H*)-ones; ketenimine

## 1. Introduction

Due to their great physiological importance and pharmaceutical usefulness for fighting tumors, quinazolin-4(3*H*)-ones are promising compounds for biological and medicinal applications [1–4]. Some natural and synthetic quinazolin-4(3*H*)-ones with therapeutic properties are already being tested in clinical trials as potential drugs. For instance, natural products like deoxyvasicinone (I) [5] and tryptanthrin (II) [6–8] (Figure 1) have demonstrated antibacterial, antidepressant, and anti-inflammatory properties. The compound 2-(4-hydroxybenzyl)quinazolin-4(3*H*)-one (HBQ, III) [9,10], which is obtained from a fungus found in marine sediment, has been shown to have significant cytotoxic activity against certain cancer cell lines as well as strong inhibitory effects on the replication of tobacco mosaic virus (TMV). Given their versatile pharmacological and biological characteristics, there is always an urgent need for the synthesis of quinazolin-4(3*H*)-one products.



**Figure 1.** Natural products containing the quinazolin-4(3*H*)-one skeleton.

Traditional methods for synthesizing quinazolin-4(3*H*)-ones involve two main approaches. One method is the amidation of benzoxazinones with arylamines [11,12]. The other method is the condensation of 2-aminobenzoyl derivatives with carbonyl derivatives (Scheme 1a). The latter method is the primary approach; the 2-aminobenzoyl



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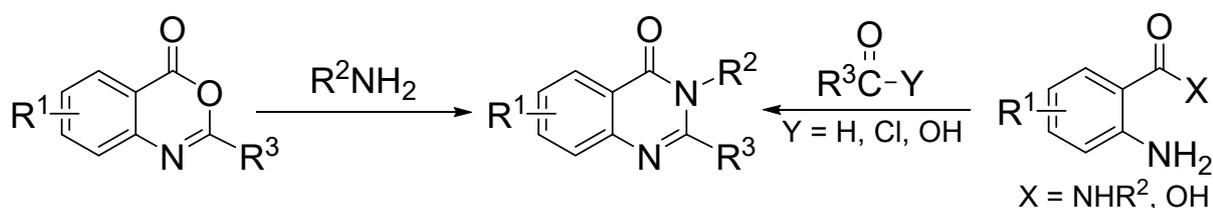
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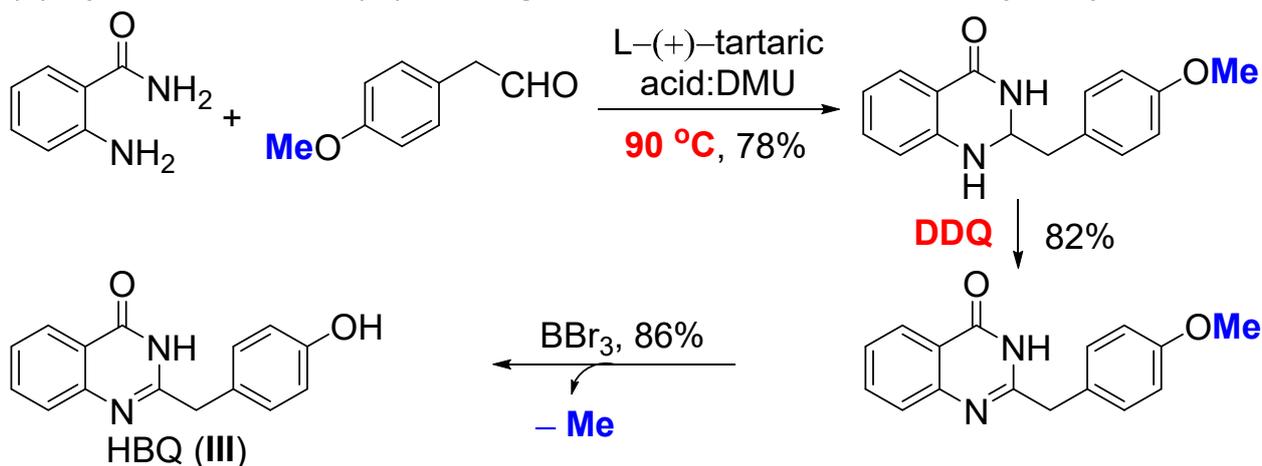
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derivatives included are 2-aminobenzamides [13–24], 2-aminobenzoic acid [11,25–27], 2-nitrobenzamides [28,29], and methyl anthranilate [30–32], while the carbonyl derivatives included are aldehydes [14,15], 1,3-diketones [16,17], orthoesters [18,19], benzyl alcohols [20–22], benzyl halides [23,24], acetophenones [33–36], methylarenes [37], and others [38,39]. Although most of these synthetic methods have their own merits, they often require extreme reaction conditions such as heating, using dehydration reagents, and adding an oxidant, which limits the synthesis of phenolic quinazolin-4(3*H*)-ones, or the phenol hydroxyl group needs to be protected in advance. For example, HBQ needs to be synthesized by oxidation from 4(1*H*) quinazolinone using DDQ, which also requires high temperatures and protection of the phenol hydroxyl group from oxidation (Scheme 1b) [15].

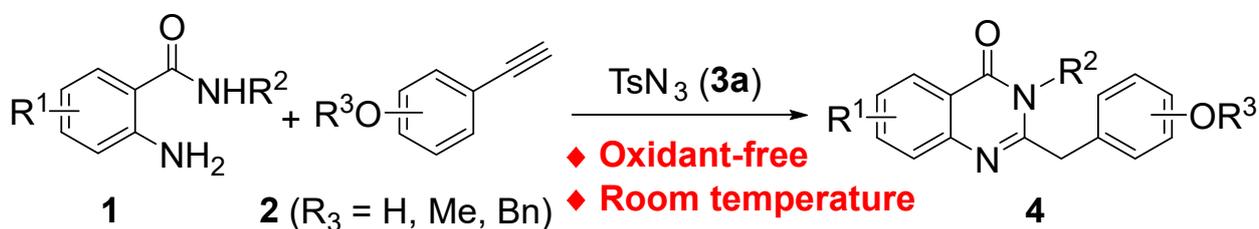
### (a) Two main synthesis strategies of quinazolin-4(3*H*)-ones



### (b) Synthesis of HBQ (III) with high temperature, oxidant, and hydroxyl protection



### (c) this work: Synthesis of quinazolinones with oxidant-free and mild condition



Scheme 1. Strategies for the synthesis of quinazolin-4(3*H*)-ones.

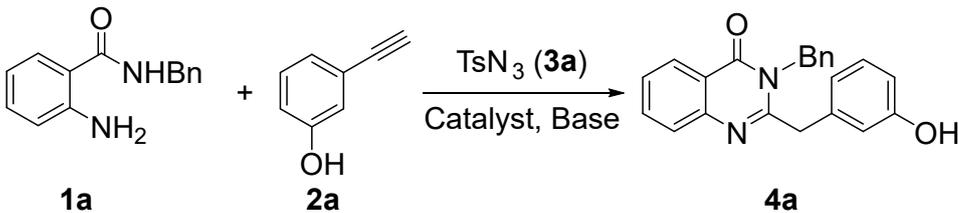
Since it was reported by Chang's group [40,41], the copper-catalyzed sulfonyl azide–alkyne cycloaddition/ring cleavage reaction (CuAAC/ring cleavage reaction) has been acknowledged as a gentle and effective method for synthesizing various nitrogenated compounds. It has also been used for modifying the structure of natural products, drugs, and biological macromolecules [42–44]. Our group has delved into this area and utilized the CuAAC/ring cleavage reaction to synthesize pyridine derivatives, fused heterocycles, coumarins, indoles, and other nitrogenated compounds [45–49].

Therefore, in this study, we present a highly efficient and oxidant-free approach to synthesize phenolic quinazolin-4(3*H*)-ones using the CuAAC/ring cleavage reaction (Scheme 1c). This method involves stirring a mixture of 2-aminobenzamides, sulfonyl azides, and terminal alkynes in the presence of a copper(I) catalyst under mild conditions.

## 2. Results

Our investigations began with an examination of the synthesis of the parent and previously unreported system 3-benzyl-2-(3-hydroxybenzyl)quinazolin-4(3*H*)-one **4a** via 2-amino-*N*-benzylbenzamide **1a**, 3-ethynylphenol **2a**, and tosyl azide **3a** (Table 1). After an initial screening using CuI as a catalyst with the additive Et<sub>3</sub>N in a variety of solvents, we found that the desired conversion was affected by different solvents (Table 1, entries 1–10). The results revealed that MeCN generated product **4a** in the highest yield of 85%, the other solvents gave comparable yields, and EtOH generated product **4a** with the lowest yield of 34%. Encouraged by these promising results, a variety of catalysts were then evaluated, as shown in Table 1 (entries 11–17). Among the copper catalysts used, Cu<sup>I</sup> catalysts (Table 1, entries 11–12) exhibited higher catalytic reactivity than Cu<sup>II</sup> catalysts (Table 1, entries 13–16), and Cu(OTf)<sub>2</sub> (Table 1, entry 17) was the least efficient for this reaction. Additional screening revealed that the other additives used were less efficient than Et<sub>3</sub>N (Table 1, entries 18–20). It is worth noting that the other sulfonyl azides such as MsN<sub>3</sub> or PhSO<sub>2</sub>N<sub>3</sub> were also suitable for this reaction (Table 1, entry 21).

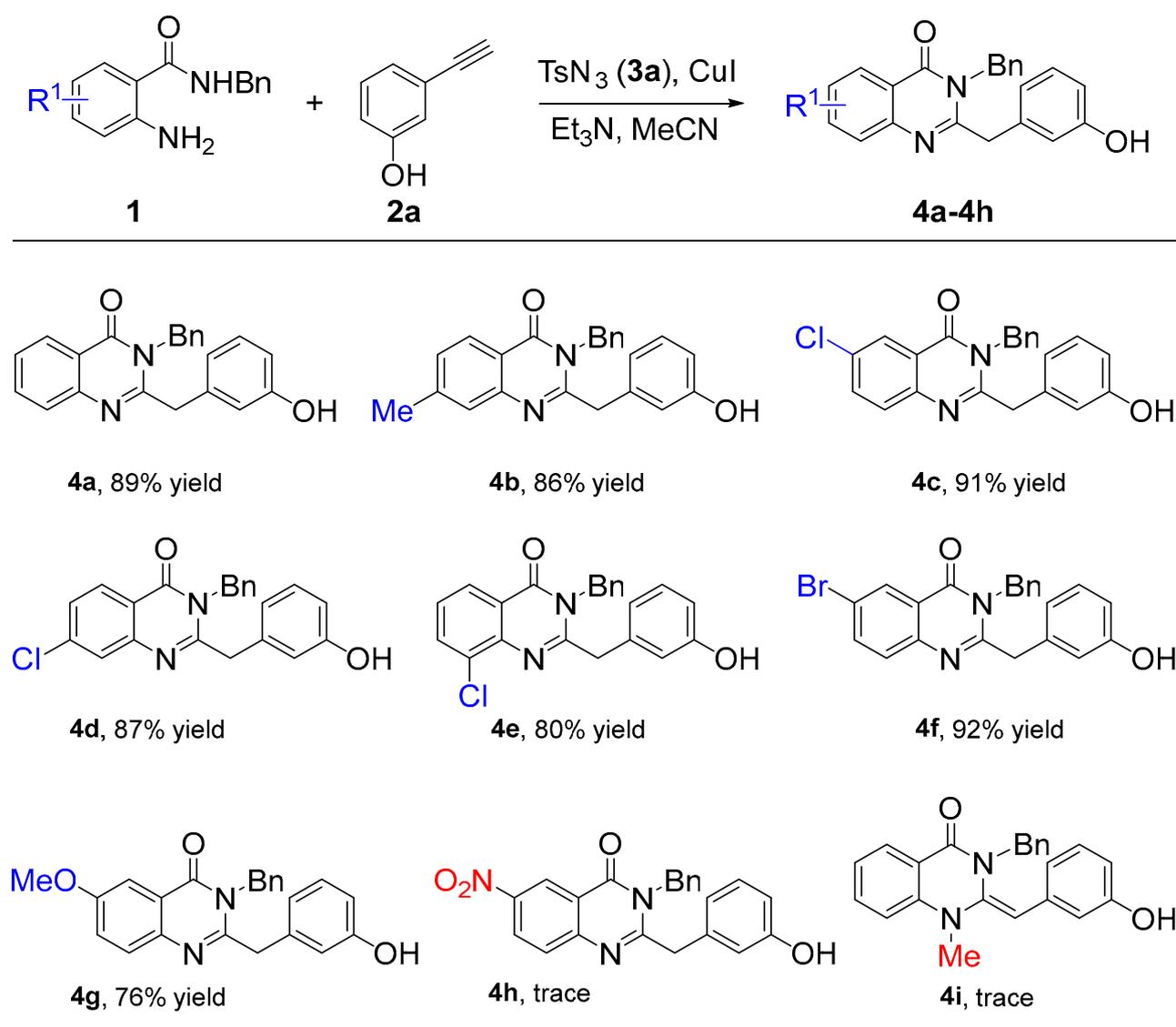
**Table 1.** Optimization of catalytic conditions <sup>a</sup>.



Entry	Cat. (10 mol%)	Base (0.11 mmol)	Solvent (2 mL)	Yield (%) <sup>b</sup>
1	CuI	Et <sub>3</sub> N	CHCl <sub>3</sub>	71
2	CuI	Et <sub>3</sub> N	DCE	74
3	CuI	Et <sub>3</sub> N	DCM	67
4	CuI	Et <sub>3</sub> N	Toluene	63
5	CuI	Et <sub>3</sub> N	MeCN	89
6	CuI	Et <sub>3</sub> N	THF	70
7	CuI	Et <sub>3</sub> N	DMSO	58
8	CuI	Et <sub>3</sub> N	DMF	63
9	CuI	Et <sub>3</sub> N	Dioxane	52
10	CuI	Et <sub>3</sub> N	EtOH	34
11	CuCl	Et <sub>3</sub> N	MeCN	85
12	CuBr	Et <sub>3</sub> N	MeCN	82
13	CuBr <sub>2</sub>	Et <sub>3</sub> N	MeCN	72
14	CuCl <sub>2</sub> ·2H <sub>2</sub> O	Et <sub>3</sub> N	MeCN	68
15	Cu(OAc) <sub>2</sub>	Et <sub>3</sub> N	MeCN	74
16	Cu(acac) <sub>2</sub>	Et <sub>3</sub> N	MeCN	44
17	Cu(OTf) <sub>2</sub>	Et <sub>3</sub> N	MeCN	22
18	CuI	DAMP	MeCN	21
19	CuI	DIPEA	MeCN	86
20	CuI	NaOH	MeCN	12
21	CuI	Et <sub>3</sub> N	MeCN	89 <sup>c</sup>

<sup>a</sup> Reaction conditions: **1a** (0.10 mmol), **2a** (0.11 mmol), and the catalyst (10 mol%) and base (0.11 mmol) in the solvent (2 mL) were added with **3a** (0.11 mmol) and stirred at room temperature for 12 h. <sup>b</sup> Isolated yields. <sup>c</sup> MsN<sub>3</sub> or PhSO<sub>2</sub>N<sub>3</sub> was used instead of TsN<sub>3</sub>.

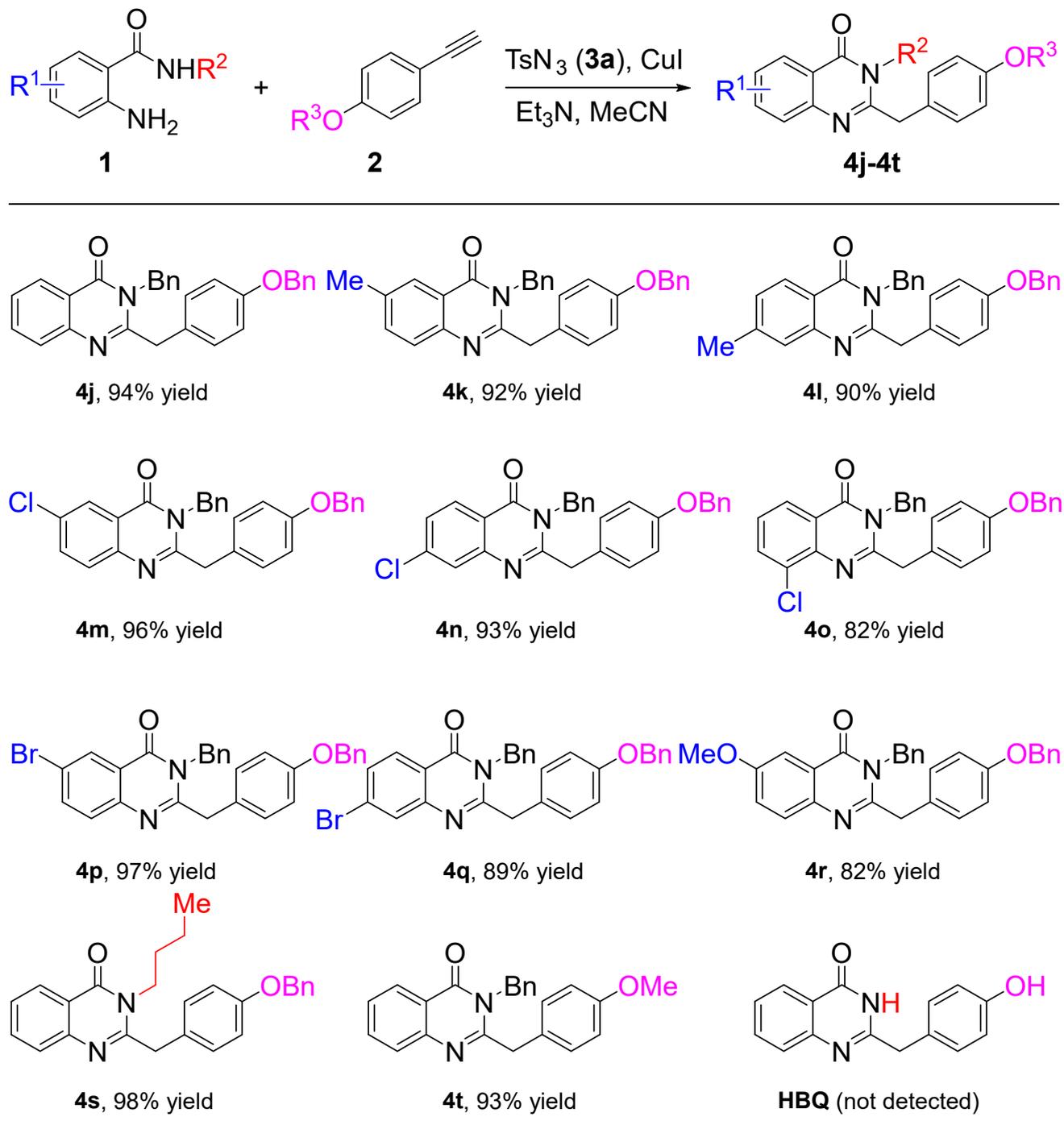
After the optimized reaction condition was established (Table 1, entry 5), the capacity of these reactions to affect the coupling of a range of different 2-aminobenzamides **1** was investigated. As shown in Scheme 2, the electronic effects of the substituents 2-aminobenzamides **1** had an obvious influence. For example, the substrate bearing a –Me group was examined, and an 82% yield of **4b** was isolated, which is the same efficiency as **4a**. When 2-aminobenzamides **1** carried halogen substituents including Cl or Br, the anticipated products (**4c–4f**) were also obtained in good yields ranging from 80% to 92%. However, the strong electron-donating substituent gave the corresponding product **4g** with a moderate yield of 76%, while the strongly electron-withdrawing substituent did not obtain the target product **4h** due to the weak nucleophilic activity of the amino group. Finally, when the –NH<sub>2</sub> group was replaced by –NHMe, the target product **4i** was not obtained.



**Scheme 2.** Substrate scope of 2-aminobenzamides **1**.

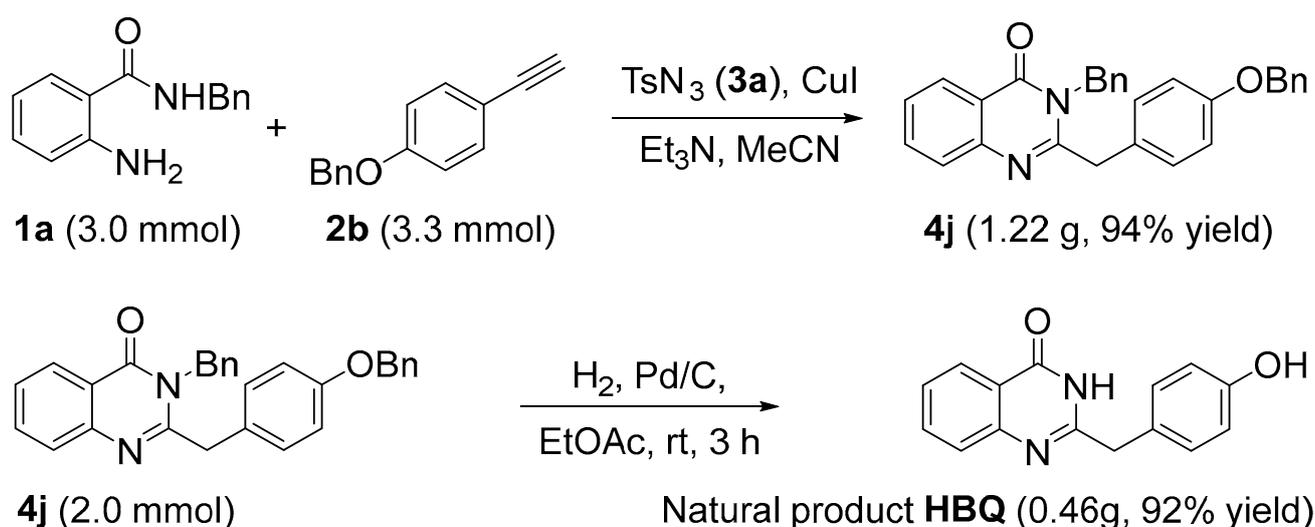
The scope and limitations of different substrates with 2-aminobenzamides **1** and terminal alkynes **2** were also tested. As shown in Scheme 3, 2-aminobenzamides **1** exhibit the same electronic effect when 1-(benzyloxy)-4-ethynylbenzene is involved as a terminal alkyne in this reaction. The effect of the –Me group on the reaction is relatively small (**4j–4l**), the halogen groups are the most effective (**4m–4q**), and the strong electron-donating group is poor (**4r**). Expectedly, with R<sup>2</sup> bearing an *n*-butyl or R<sup>3</sup> bearing a –Me group, the corre-

sponding quinazolin-4(3*H*)-one derivatives **4s** or **4t** are formed in an excellent yield of 98% and 93%, respectively. Disappointingly, the natural product 2-(4-hydroxybenzyl)quinazolin-4(3*H*)-one (HBQ, Figure 1, III) was not obtained when the R<sup>2</sup> group changed to H of **1a**, which shows that the proton in this situation interferes with the reaction.



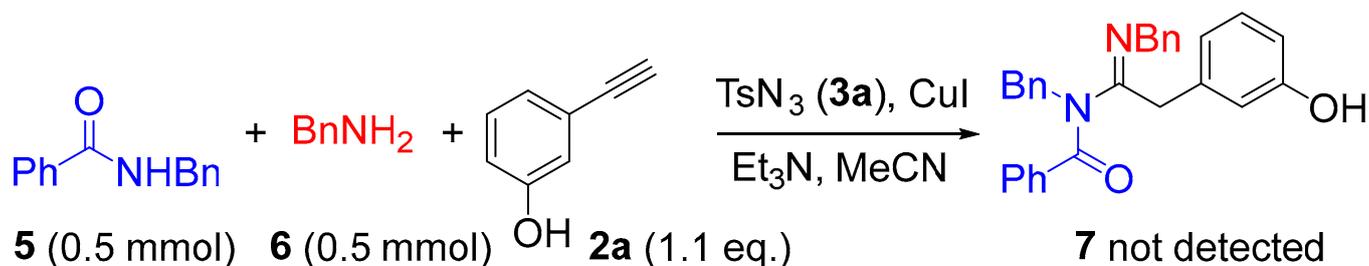
**Scheme 3.** Substrate scope of 2-aminobenzamides **1** and terminal alkynes **2**.

Although the natural product HBQ cannot be directly obtained by the above method, it can be obtained by a simple reduction of product **4j** and can also be prepared in large quantities under mild conditions (Scheme 4).



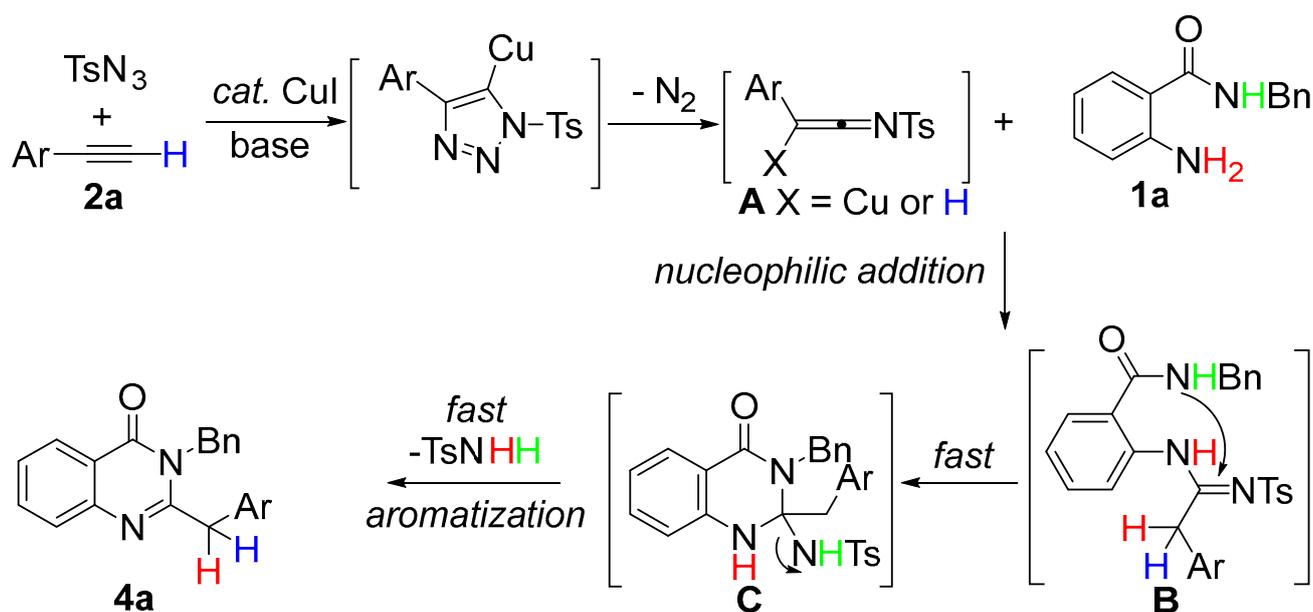
**Scheme 4.** Synthesis of natural product HBQ.

What is interesting to us is that there was no sulfonyl group in the target products, and we could not detect the other undesired product  $\text{TsNH}_2$ , which we compared with standard samples by thin-layer chromatography (TLC) and confirmed by NMR. Moreover, unlike the other products, compound **4i**, which was difficult to synthesize (Scheme 2), was unaromatized. Therefore, we concluded that the product had aromatic properties. To confirm this fact and elucidate the mechanism, an intermolecular control experiment was performed under the optimized reaction condition (Table 1, entry 5). As shown in Scheme 5, *N*-Phenylbenzamide **5** and benzylamine **6** were tested for the intermolecular reaction. After being detected by TLC and confirmed by NMR, the *N*-sulfonylamidine product, which has been reported previously [41], was formed instead of the desired compound **7**. The above experiments show that aromaticity is indispensable.



**Scheme 5.** Control experiment.

Based on the above experiments, a possible reaction pathway for the synthesis of quinazolin-4(3*H*)-one **4a** was proposed (Scheme 6). According to the previous proposal [41–50], *N*-sulfonylketenimine **A** was generated first by the reaction of  $\text{TsN}_3$  and **2a**. Then, **A** underwent a nucleophilic addition reaction with **1a** to generate the intermediate **B**. Subsequently, intermediate **B** underwent an intramolecular cascade addition to generate the intermediate **C**. Lastly, the desired product **4a** and product  $\text{TsNH}_2$  were obtained by aromatization of intermediate **C**. We could not detect intermediates **B** and **C** during the experiment, which indicated that the procedure from **B** to **4a** was fast and almost simultaneous. The sulfonyl group was eliminated through the power of aromatization and activated the decomposition of the terminal alkynes into  $\text{TsNH}_2$  and  $\text{N}_2$ .



**Scheme 6.** Plausible reaction mechanism.

### 3. Experimental Procedure

#### 3.1. General Information

The  $^1\text{H}$  NMR spectra were recorded on a Bruker DPX 400 MHz spectrometer in  $\text{CDCl}_3$ . Chemical shifts are reported in ppm with the internal TMS signal at 0.0 ppm as a standard. The spectra were interpreted as s, singlet; bs, broad singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, double doublet; ddd, double double doublet; dt, double triplet; ddt, double double triplet; tt, triple triplet; td, triple doublet. Coupling constant(s)  $J$  are reported in Hz and relative integrations are reported. The  $^{13}\text{C}$  NMR (100 MHz) spectra were recorded on a Bruker DPX 400 MHz spectrometer in  $\text{CDCl}_3$ . Chemical shifts are reported in ppm with the internal chloroform signal at 77.16 ppm as a standard and HBQ using  $\text{CD}_3\text{OD}$  residual nondeuterated solvent as internal standard ( $\text{CD}_3\text{OD}$ :  $\delta$  3.31 for  $^1\text{H}$  and 49.00 ppm for  $^{13}\text{C}$ ). Melting points were obtained in open capillary tubes using the SGW X-4 micro melting point apparatus and were uncorrected. IR spectra were obtained with the Bruker Tensor-27 FT-IR spectrometer. Mass spectra were recorded on a TOF mass spectrometer. The starting materials, 2-amino-*N*-benzylbenzamide derivatives **1**, were all known and prepared according to the literature procedures [50,51]. Terminal alkynes **2**,  $\text{TsN}_3$  **3a**, and other reagents were purchased from Adamas-beta and other suppliers and used without further purification.

#### 3.2. Compound Characterization and Preparations

At room temperature, to a solution of 2-amino-*N*-benzylbenzamides **1** (0.1 mmol, 1.0 equiv.), phenyl acetylenes **2** (0.11 mmol, 1.1 equiv.),  $\text{CuI}$  (1.9 mg, 10 mol%),  $\text{TsN}_3$  **3a** (21.7 mg, 0.11 mmol, 1.1 equiv.), and  $\text{Et}_3\text{N}$  (11.1 mg, 0.11 mmol, 1.1 equiv.) in MeCN (2 mL) was added. The reaction mixture was stirred for 12 h. After completion of the reaction as indicated by TLC, the solvent was removed by evaporation in a vacuum. The residue was directly purified by flash column chromatography on silica gel (eluting with hexanes/ $\text{EtOAc}$  = 2:1) to form the corresponding product **4**. Some products contained the impurity sulfonamide which is difficult to separate when generated in this reaction.

*3-Benzyl-2-(3-hydroxybenzyl)quinazolin-4(3H)-one (4a)*. White solid, 30.5 mg, yield: 89%, m.p: 180–182 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  9.86 (s, 1H), 8.08–7.93 (m, 1H), 7.59–7.52 (m, 1H), 7.42 (dt,  $J$  = 9.6, 4.7 Hz, 2H), 7.36–7.20 (m, 4H), 7.10 (d,  $J$  = 7.2 Hz, 2H), 6.82 (d,  $J$  = 5.4 Hz, 2H), 6.74 (d,  $J$  = 7.7 Hz, 1H), 5.13 (s, 2H), 4.00 (s, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  161.8, 158.3, 156.8, 145.2, 135.8 (2C), 134.9, 131.0, 129.2 (2C), 128.0, 127.9, 127.5, 126.4 (2C), 124.9,

119.8, 119.7, 115.4, 113.6, 46.3, 41.5; IR  $\nu_{\max}$  (KBr): 3308, 2928, 1682, 1591, 1456, 1265, 1165, 976, 775, 731  $\text{cm}^{-1}$ ; HRMS (ESITOF)  $m/z$  calcd for  $\text{C}_{22}\text{H}_{18}\text{N}_2\text{O}_2$ ,  $[\text{M} + \text{H}]^+$  343.1441, found 343.1443.

**3-Benzyl-2-(3-hydroxybenzyl)-7-methylquinazolin-4(3H)-one (4b).** White solid, 30.6 mg, yield: 86%, m.p: 184–186 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  9.86 (s, 1H), 7.90 (dd,  $J = 8.5, 2.9$  Hz, 1H), 7.38–7.28 (m, 3H), 7.27–7.20 (m, 2H), 7.15 (d,  $J = 2.5$  Hz, 1H), 7.13–7.08 (m, 2H), 6.80 (d,  $J = 4.9$  Hz, 2H), 6.73 (d,  $J = 7.6$  Hz, 1H), 5.12 (s, 2H), 3.97 (s, 2H), 2.37 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  161.7, 158.4, 156.8, 146.4, 145.4, 136.0, 135.9, 130.9, 129.9, 129.2, 129.0, 128.0, 127.8, 126.6, 126.4, 124.6, 119.7, 117.3, 115.3, 113.6, 46.0, 41.4, 22.1; IR  $\nu_{\max}$  (KBr): 3055, 1682, 1592, 1456, 1342, 1265, 1163, 974, 879, 737  $\text{cm}^{-1}$ ; HRMS (ESITOF)  $m/z$  calcd for  $\text{C}_{23}\text{H}_{20}\text{N}_2\text{O}_2$ ,  $[\text{M} + \text{H}]^+$  357.1598, found 357.1599.

**3-Benzyl-6-chloro-2-(3-hydroxybenzyl)quinazolin-4(3H)-one (4c).** white solid, 34.2 mg, yield: 91%, m.p: 197–199 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  9.23 (s, 1H), 8.11 (d,  $J = 2.6$  Hz, 1H), 7.50 (dt,  $J = 8.3, 2.5$  Hz, 1H), 7.37–7.21 (m, 5H), 7.10 (dd,  $J = 7.7, 3.2$  Hz, 2H), 6.81 (d,  $J = 8.5$  Hz, 1H), 6.78–6.72 (m, 2H), 5.15 (s, 2H), 4.00 (s, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  160.9, 158.1, 157.2, 143.9, 135.7, 135.5, 135.4, 133.5, 131.1, 129.3 (2C), 128.2, 127.0, 126.7, 126.5 (2C), 120.9, 120.0, 115.5, 113.5, 46.5, 41.5; IR  $\nu_{\max}$  (KBr): 3034, 2947, 1688, 1587, 1473, 1277, 1155, 980, 764, 717  $\text{cm}^{-1}$ ; HRMS (ESITOF)  $m/z$  calcd for  $\text{C}_{22}\text{H}_{17}\text{ClN}_2\text{O}_2$ ,  $[\text{M} + \text{H}]^+$  377.1051, found 377.1056.

**3-Benzyl-7-chloro-2-(3-hydroxybenzyl)quinazolin-4(3H)-one (4d).** white solid, 32.7 mg, yield: 87%, m.p: 190–192 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.23 (s, 1H), 8.14–8.03 (m, 1H), 7.47 (d,  $J = 2.7$  Hz, 1H), 7.44–7.38 (m, 1H), 7.37–7.29 (m, 3H), 7.28–7.22 (m, 1H), 7.13 (d,  $J = 7.1$  Hz, 2H), 6.81 (d,  $J = 8.3$  Hz, 1H), 6.75 (d,  $J = 15.3$  Hz, 2H), 5.17 (s, 2H), 4.00 (s, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  161.3, 156.0, 157.7, 146.8, 141.3, 135.8, 135.7, 131.0, 129.3 (2C), 129.2, 128.1 (2C), 126.4 (2C), 125.3, 120.2, 118.5, 115.4, 113.9, 46.5, 41.7; IR  $\nu_{\max}$  (KBr): 2924, 1684, 1601, 1456, 1331, 1232, 1265, 1159, 974, 731  $\text{cm}^{-1}$ ; HRMS (ESITOF)  $m/z$  calcd for  $\text{C}_{22}\text{H}_{17}\text{ClN}_2\text{O}_2$ ,  $[\text{M} + \text{H}]^+$  377.1051, found 377.1056.

**3-Benzyl-8-chloro-2-(3-hydroxybenzyl)quinazolin-4(3H)-one (4e).** white solid, 30.1 mg, yield: 80%, m.p: 197–199 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.21 (dd,  $J = 8.1, 3.0$  Hz, 1H), 7.75 (dd,  $J = 7.9, 3.0$  Hz, 1H), 7.42–7.27 (m, 4H), 7.18 (td,  $J = 7.7, 7.2, 4.2$  Hz, 1H), 7.13 (d,  $J = 7.5$  Hz, 2H), 6.83 (s, 1H), 6.75 (t,  $J = 9.9$  Hz, 2H), 5.98 (s, 1H), 5.25 (s, 2H), 4.09 (s, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  162.2, 156.9, 156.7, 143.9, 136.5, 135.8, 134.9, 131.4, 130.5, 129.2 (2C), 128.0, 127.1, 126.3 (2C), 126.2, 122.2, 120.5, 115.1, 114.8, 46.6, 41.9; IR  $\nu_{\max}$  (KBr): 3007, 1676, 1580, 1445, 1389, 1275, 1159, 980, 849, 764  $\text{cm}^{-1}$ ; HRMS (ESITOF)  $m/z$  calcd for  $\text{C}_{22}\text{H}_{17}\text{ClN}_2\text{O}_2$ ,  $[\text{M} + \text{H}]^+$  377.1051, found 377.1056.

**3-Benzyl-6-bromo-2-(3-hydroxybenzyl)quinazolin-4(3H)-one (4f).** white solid, 38.6 mg, yield: 92%, m.p: 176–178 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  9.33 (s, 1H), 8.30 (q,  $J = 2.2$  Hz, 1H), 7.68–7.57 (m, 1H), 7.38–7.21 (m, 5H), 7.10 (d,  $J = 7.2$  Hz, 2H), 6.81 (d,  $J = 8.4$  Hz, 1H), 6.75 (d,  $J = 10.2$  Hz, 2H), 5.15 (s, 2H), 4.00 (s, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  160.7, 158.2, 157.4, 144.2, 138.2, 135.6, 135.5, 131.1, 130.3, 129.3 (2C), 128.2, 126.7, 126.5 (2C), 121.3, 121.2, 120.0, 115.5, 113.4, 46.5, 41.5; IR  $\nu_{\max}$  (KBr): 3026, 1684, 1587, 1456, 1389, 1277, 1153, 966, 831, 750  $\text{cm}^{-1}$ ; HRMS (ESITOF)  $m/z$  calcd for  $\text{C}_{22}\text{H}_{17}\text{BrN}_2\text{O}_2$ ,  $[\text{M} + \text{H}]^+$  421.0546, found 421.0551.

**3-Benzyl-2-(3-hydroxybenzyl)-6-methoxyquinazolin-4(3H)-one (4g).** White solid, 28.3 mg, yield: 76%, m.p: 183–185 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  10.06 (s, 1H), 7.42 (q,  $J = 2.7$  Hz, 1H), 7.37–7.19 (m, 5H), 7.11 (td,  $J = 5.6, 2.7$  Hz, 3H), 6.81 (d,  $J = 2.8$  Hz, 2H), 6.73 (d,  $J = 7.6$  Hz, 1H), 5.13 (s, 2H), 3.99 (s, 2H), 3.97 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  161.7, 158.5, 158.4, 154.4, 139.6, 136.1, 136.0, 130.9, 129.8, 129.2, 128.0, 126.6, 126.4 (2C), 124.1, 120.8, 119.7, 115.4, 113.6, 108.1, 55.8, 46.4, 41.2; IR  $\nu_{\max}$  (KBr): 3005, 1670, 1593, 1495, 1456, 1362, 1275, 1155, 1028, 750  $\text{cm}^{-1}$ ; HRMS (ESITOF)  $m/z$  calcd for  $\text{C}_{23}\text{H}_{20}\text{N}_2\text{O}_3$ ,  $[\text{M} + \text{H}]^+$  373.1547, found 373.1549.

3-Benzyl-2-(4-(benzyloxy)benzyl)quinazolin-4(3H)-one (**4j**). Oil, 40.6 mg, yield: 94%.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.33 (dd,  $J = 8.1, 2.8$  Hz, 1H), 7.82–7.70 (m, 2H), 7.50 (d,  $J = 8.1$  Hz, 1H), 7.44–7.21 (m, 8H), 7.17–7.11 (m, 4H), 6.93 (dd,  $J = 7.8, 3.1$  Hz, 2H), 5.26 (s, 2H), 5.04 (s, 2H), 4.02 (s, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  162.8, 158.2, 155.9, 147.4, 136.9, 136.3, 134.6, 129.3 (2C), 129.1 (2C), 128.7 (2C), 128.1, 127.7, 127.6 (2C), 127.5, 127.4, 127.3, 127.0, 126.3 (2C), 120.6, 115.6 (2C), 70.2, 46.3, 41.6; IR  $\nu_{\text{max}}$  (KBr): 3032, 1672, 1591, 1508, 1454, 1240, 1172, 1013, 750, 694  $\text{cm}^{-1}$ ; HRMS (ESITOF)  $m/z$  calcd for  $\text{C}_{29}\text{H}_{24}\text{N}_2\text{O}_2$ ,  $[\text{M} + \text{H}]^+$  433.1911, found 433.1910.

3-Benzyl-2-(4-(benzyloxy)benzyl)-6-methylquinazolin-4(3H)-one (**4k**). White solid, 41.1 mg, yield: 92%, m.p.: 137–139 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.12 (s, 1H), 7.64 (dd,  $J = 8.3, 2.8$  Hz, 1H), 7.61–7.57 (m, 1H), 7.45–7.22 (m, 8H), 7.13 (d,  $J = 7.3$  Hz, 4H), 6.92 (dd,  $J = 8.3, 3.0$  Hz, 2H), 5.26 (s, 2H), 5.04 (s, 2H), 4.01 (s, 2H), 2.50 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  162.9, 158.2, 155.0, 145.5, 137.2, 137.0, 136.4, 136.0, 129.2 (2C), 129.1 (2C), 128.7 (2C), 128.1, 127.7 (2C), 127.6 (2C), 127.2, 126.7, 126.3 (2C), 120.4, 115.6 (2C), 70.2, 46.2, 41.5, 21.5; IR  $\nu_{\text{max}}$  (KBr): 3032, 1670, 1591, 1508, 1454, 1340, 1275, 1013, 831, 750  $\text{cm}^{-1}$ ; HRMS (ESITOF)  $m/z$  calcd for  $\text{C}_{30}\text{H}_{26}\text{N}_2\text{O}_2$ ,  $[\text{M} + \text{H}]^+$  447.2067, found 447.2069.

3-Benzyl-2-(4-(benzyloxy)benzyl)-7-methylquinazolin-4(3H)-one (**4l**). Oil, 40.2 mg, yield: 90%.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.21 (dd,  $J = 8.5, 3.0$  Hz, 1H), 7.54 (s, 1H), 7.44–7.23 (m, 9H), 7.13 (d,  $J = 7.2$  Hz, 4H), 6.95–6.89 (m, 2H), 5.25 (s, 2H), 5.03 (s, 2H), 4.00 (s, 2H), 2.51 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  162.8, 158.2, 155.9, 147.5, 145.6, 137.0, 136.5, 129.3 (2C), 129.1 (2C), 128.7 (2C), 128.5, 128.1, 127.7, 127.6, 127.5 (2C), 127.1, 127.0, 126.3 (2C), 118.2, 115.6 (2C), 70.2, 46.1, 41.6, 22.0; IR  $\nu_{\text{max}}$  (KBr): 3032, 1672, 1593, 1508, 1454, 1259, 1173, 1011, 750, 696  $\text{cm}^{-1}$ ; HRMS (ESITOF)  $m/z$  calcd for  $\text{C}_{30}\text{H}_{26}\text{N}_2\text{O}_2$ ,  $[\text{M} + \text{H}]^+$  447.2067, found 447.2069.

3-Benzyl-2-(4-(benzyloxy)benzyl)-6-chloroquinazolin-4(3H)-one (**4m**). White solid, 44.7 mg, yield: 96%, m.p.: 174–176 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.20 (s, 1H), 7.66–7.55 (m, 2H), 7.38–7.15 (m, 8H), 7.04 (dd,  $J = 8.1, 2.9$  Hz, 4H), 6.85 (dd,  $J = 8.7, 3.0$  Hz, 2H), 5.17 (s, 2H), 4.96 (s, 2H), 3.93 (s, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  161.9, 158.3, 156.2, 146.0, 136.9, 136.0, 135.0, 132.7, 129.3 (2C), 129.2 (2C), 129.1, 128.7 (2C), 128.2, 127.9, 127.6 (2C), 127.2, 126.6, 126.3 (2C), 121.7, 115.6 (2C), 70.2, 46.4, 41.5; IR  $\nu_{\text{max}}$  (KBr): 3034, 1676, 1591, 1508, 1472, 1335, 1275, 1013, 835, 750  $\text{cm}^{-1}$ ; HRMS (ESITOF)  $m/z$  calcd for  $\text{C}_{29}\text{H}_{23}\text{ClN}_2\text{O}_2$ ,  $[\text{M} + \text{H}]^+$  467.1521, found 467.1528.

3-Benzyl-2-(4-(benzyloxy)benzyl)-7-chloroquinazolin-4(3H)-one (**4n**). Oil, 43.4 mg, yield: 93%.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.24 (dd,  $J = 9.0, 3.1$  Hz, 1H), 7.73 (d,  $J = 3.0$  Hz, 1H), 7.47–7.23 (m, 9H), 7.13 (d,  $J = 6.8$  Hz, 4H), 6.93 (dd,  $J = 8.1, 3.2$  Hz, 2H), 5.25 (s, 2H), 5.04 (s, 2H), 4.00 (s, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  162.3, 158.3, 157.3, 148.4, 140.8, 136.9, 136.1, 129.3 (2C), 129.2 (2C), 128.8, 128.7 (2C), 128.2, 127.9, 127.6 (2C), 127.5, 127.2, 127.0, 126.3 (2C), 119.1, 115.6 (2C), 70.2, 46.3, 41.5; IR  $\nu_{\text{max}}$  (KBr): 3034, 1676, 1591, 1508, 1454, 1383, 1240, 1013, 748, 694  $\text{cm}^{-1}$ ; HRMS (ESITOF)  $m/z$  calcd for  $\text{C}_{29}\text{H}_{23}\text{ClN}_2\text{O}_2$ ,  $[\text{M} + \text{H}]^+$  467.1521, found 467.1528.

3-Benzyl-2-(4-(benzyloxy)benzyl)-8-chloroquinazolin-4(3H)-one (**4o**). White solid, 38.2 mg, yield: 82%, m.p.: 111–113 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.22 (dd,  $J = 8.0, 2.8$  Hz, 1H), 7.84 (dd,  $J = 7.9, 2.8$  Hz, 1H), 7.44–7.35 (m, 5H), 7.34–7.26 (m, 4H), 7.16 (d,  $J = 7.8$  Hz, 2H), 7.12 (d,  $J = 6.7$  Hz, 2H), 6.93 (dd,  $J = 8.0, 2.6$  Hz, 2H), 5.26 (s, 2H), 5.04 (s, 2H), 4.07 (s, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  162.3, 158.3, 156.8, 144.2, 137.0, 135.9, 134.8, 129.5 (2C), 129.2 (2C), 128.91, 128.7 (2C), 128.1, 127.9, 127.6 (2C), 127.3, 126.9, 126.3 (2C), 126.1, 122.2, 115.6 (2C), 70.2, 46.5, 41.7; IR  $\nu_{\text{max}}$  (KBr): 3030, 1676, 1591, 1508, 1445, 1261, 1163, 987, 748, 696  $\text{cm}^{-1}$ ; HRMS (ESITOF)  $m/z$  calcd for  $\text{C}_{29}\text{H}_{23}\text{ClN}_2\text{O}_2$ ,  $[\text{M} + \text{H}]^+$  467.1521, found 467.1528.

3-Benzyl-2-(4-(benzyloxy)benzyl)-6-bromoquinazolin-4(3H)-one (**4p**). White solid, 49.5 mg, yield: 97%, m.p.: 167–169 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.45 (t,  $J = 2.4$  Hz, 1H), 7.83 (dd,  $J = 8.7, 2.6$  Hz, 1H), 7.59 (dd,  $J = 9.4, 3.0$  Hz, 1H), 7.44–7.29 (m, 8H), 7.12 (d,  $J = 6.8$  Hz, 4H), 6.93 (dd,  $J = 7.8, 2.8$  Hz, 2H), 5.25 (s, 2H), 5.04 (s, 2H), 4.00 (s, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  161.7, 158.3, 156.3, 146.3, 137.7, 136.9, 136.0, 129.8, 129.3 (2C), 129.2, 129.1 (2C), 128.7 (2C), 128.2, 127.9, 127.6 (2C), 127.2, 126.3 (2C), 122.0, 120.4, 115.6 (2C), 70.2, 46.4, 41.5;

IR  $\nu_{\max}$  (KBr): 2905, 1676, 1589, 1510, 1467, 1333, 1275, 985, 750, 692  $\text{cm}^{-1}$ ; HRMS (ESITOF)  $m/z$  calcd for  $\text{C}_{29}\text{H}_{23}\text{BrN}_2\text{O}_2$ ,  $[\text{M} + \text{H}]^+$  511.1016, found 511.1021.

**3-Benzyl-2-(4-(benzyloxy)benzyl)-7-bromoquinazolin-4(3H)-one (4q)**. Oil, 45.4 mg, yield: 89%.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.16 (dd,  $J = 8.8, 3.0$  Hz, 1H), 7.91 (s, 1H), 7.58 (dd,  $J = 8.6, 2.7$  Hz, 1H), 7.45–7.23 (m, 8H), 7.13 (d,  $J = 6.9$  Hz, 4H), 6.97–6.90 (m, 2H), 5.25 (s, 2H), 5.04 (s, 2H), 4.00 (s, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  162.4, 158.3, 157.3, 148.4, 136.9, 136.0, 130.3, 130.2, 129.4 (2C), 129.3, 129.2 (2C), 128.8, 128.7 (2C), 128.2, 127.9, 127.6 (2C), 127.2, 126.3 (2C), 119.5, 115.6 (2C), 70.2, 46.4, 41.5; IR  $\nu_{\max}$  (KBr): 3032, 1676, 1591, 1508, 1454, 1259, 1013, 883, 750, 694  $\text{cm}^{-1}$ ; HRMS (ESITOF)  $m/z$  calcd for  $\text{C}_{29}\text{H}_{23}\text{BrN}_2\text{O}_2$ ,  $[\text{M} + \text{H}]^+$  511.1016, found 511.1021.

**3-Benzyl-2-(4-(benzyloxy)benzyl)-6-methoxyquinazolin-4(3H)-one (4r)**. Oil, 37.9 mg, yield: 82%.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.72–7.64 (m, 2H), 7.44–7.25 (m, 9H), 7.13 (dd,  $J = 8.3, 3.0$  Hz, 4H), 6.96–6.90 (m, 2H), 5.27 (s, 2H), 5.03 (s, 2H), 4.01 (s, 2H), 3.91 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  162.7, 158.5, 158.2, 153.5, 142.1, 137.0, 136.4, 129.2 (2C), 129.1 (2C), 129.0, 128.7 (2C), 128.1, 127.8, 127.7, 127.6 (2C), 126.3 (2C), 124.9, 121.4, 115.5 (2C), 106.5, 70.2, 55.9, 46.4, 41.4; IR  $\nu_{\max}$  (KBr): 3032, 1667, 1591, 1489, 1360, 1240, 1026, 837, 750, 694  $\text{cm}^{-1}$ ; HRMS (ESITOF)  $m/z$  calcd for  $\text{C}_{30}\text{H}_{26}\text{N}_2\text{O}_3$ ,  $[\text{M} + \text{H}]^+$  463.2016, found 463.2022.

**2-(4-(Benzyloxy)benzyl)-3-butylquinazolin-4(3H)-one (4s)**. Oil, 39.0 mg, yield: 98%.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.26 (dd,  $J = 8.1, 2.9$  Hz, 1H), 7.72 (tt,  $J = 8.3, 5.3$  Hz, 2H), 7.49–7.43 (m, 1H), 7.43–7.28 (m, 5H), 7.18 (d,  $J = 7.7$  Hz, 2H), 6.93 (dd,  $J = 7.9, 2.8$  Hz, 2H), 5.04 (s, 2H), 4.18 (s, 2H), 4.01–3.88 (m, 2H), 1.60–1.49 (m, 2H), 1.36 (q,  $J = 7.5$  Hz, 2H), 0.92 (td,  $J = 7.8, 2.5$  Hz, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  162.5, 158.2, 155.6, 147.4, 137.0, 134.3, 129.4 (2C), 128.7 (2C), 128.1, 127.8, 127.6 (2C), 127.2, 126.9, 126.7, 120.9, 115.5 (2C), 70.2, 44.4, 41.8, 30.9, 20.4, 13.8; IR  $\nu_{\max}$  (KBr): 3034, 1672, 1589, 1510, 1474, 1259, 1175, 1022, 750, 696  $\text{cm}^{-1}$ ; HRMS (ESITOF)  $m/z$  calcd for  $\text{C}_{26}\text{H}_{26}\text{N}_2\text{O}_2$ ,  $[\text{M} + \text{H}]^+$  399.2067, found 399.2065.

**3-Benzyl-2-(4-methoxybenzyl)quinazolin-4(3H)-one (4t)**. Oil, 33.1 mg, yield: 93%.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.33 (dd,  $J = 8.1, 3.0$  Hz, 1H), 7.75 (td,  $J = 9.6, 8.2, 3.9$  Hz, 2H), 7.50 (t,  $J = 7.1$  Hz, 1H), 7.37–7.23 (m, 3H), 7.16–7.12 (m, 4H), 6.86 (dt,  $J = 8.8, 2.1$  Hz, 2H), 5.26 (s, 2H), 4.03 (s, 2H), 3.79 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  162.9, 159.0, 155.9, 147.5, 136.3, 134.6, 129.2 (2C), 129.1 (2C), 127.7, 127.4, 127.3, 127.2, 127.0, 126.3 (2C), 120.7, 114.7 (2C), 55.4, 46.3, 41.6; IR  $\nu_{\max}$  (KBr): 3032, 1672, 1593, 1510, 1454, 1246, 1175, 1030, 750, 694  $\text{cm}^{-1}$ ; HRMS (ESITOF)  $m/z$  calcd for  $\text{C}_{23}\text{H}_{20}\text{N}_2\text{O}_2$ ,  $[\text{M} + \text{H}]^+$  357.1598, found 357.1599.

### Gram-Scale Synthesis and Synthesis of HBQ

**3-Benzyl-2-(4-(benzyloxy)benzyl)quinazolin-4(3H)-one (4j)**. CuI (48 mg, 10 mol%) was added to an oven-dried 50 mL round-bottomed flask containing a mixture of 2-amino-*N*-benzylbenzamide **1a** (678 mg, 3.0 mmol, 1.0 equiv.), 1-(benzyloxy)-4-ethynylbenzene **2b** (686 mg, 3.3 mmol, 1.1 equiv.),  $\text{TsN}_3$  **3a** (650 mg, 3.3 mmol, 1.1 equiv.), and  $\text{Et}_3\text{N}$  (333 mg, 3.3 mmol, 1.1 equiv.) in MeCN (20 mL). The reaction mixture was stirred for 12 h. After completion of the reaction as indicated by TLC, the solvent was removed by evaporation in a vacuum. The residue was directly purified by flash column chromatography on silica gel (eluting with hexanes/EtOAc = 2:1) to obtain **4j** (1.22 g, 94% yield) as oil.

**2-(4-Hydroxybenzyl)quinazolin-4(3H)-one (HBQ)**. To a stirred solution of **4j** (0.86 g, 2.0 mmol, 1.0 equiv.) in dry EtOAc (15 mL) was added palladium (10%) on carbon (15.0 mg). Then, the reaction mixture was stirred under an atmosphere of  $\text{H}_2$  at room temperature for 3 h. The reaction mixture was then filtered on a silica pad and rinsed with EtOAc. After evaporation of the solvent, the residue was purified by flash column chromatography on silica gel (eluting with petroleum ether/EtOAc = 1:1) to obtain **HBQ** as a white solid, 460 mg, yield: 92%, m.p.: 210–212  $^\circ\text{C}$  (literature [15], m.p.: no report).  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  8.17 (dd,  $J = 8.2, 2.9$  Hz, 1H), 7.84–7.76 (m, 1H), 7.71–7.65 (m, 1H), 7.50 (td,  $J = 7.8, 2.9$  Hz, 1H), 7.22–7.15 (m, 2H), 6.75 (dt,  $J = 8.7, 2.1$  Hz, 2H), 4.57 (s, 1H), 3.90 (s, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  164.4, 158.4, 157.8, 150.1, 136.0, 130.9 (2C), 127.8, 127.7, 127.6, 127.1, 121.8, 116.6

(2C), 41.5; IR  $\nu_{\max}$  (KBr): 3383, 2492, 1682, 1609, 1452, 1269, 1119, 972, 827, 756  $\text{cm}^{-1}$ ; HRMS (ESITOF)  $m/z$  calcd for  $\text{C}_{15}\text{H}_{12}\text{N}_2\text{O}_2$ ,  $[\text{M} + \text{H}]^+$  253.0972, found 253.0969.

#### 4. Conclusions

We have developed an oxidant-free and highly effective approach to synthesize phenolic quinazolin-4(3H)-ones via the CuAAC/ring cleavage reaction. *N*-sulfonylketenimine, generated by  $\text{TsN}_3$  and terminal alkynes, undergoes two nucleophilic additions by benzamides and anilines, and the sulfonyl group is eliminated through aromatization. More importantly, the protocol can be used to synthesize the natural product 2-(4-hydroxybenzyl)quinazolin-4(3H)-one and scaled up under mild conditions. Moreover, we expect that this methodology can be applied to building phenolic quinazolin-4(3H)-one block facility.

**Supplementary Materials:** The following are available online at <https://www.mdpi.com/article/10.3390/molecules28155734/s1>. References [50,51] are cited in the supplementary materials.

**Author Contributions:** Conceptualization, methodology and supervision, X.L., X.C. and W.Y.; experiment, Y.H. and Z.Y.; spectroscopic characterization, Z.Y. and D.L.; writing—review and editing, X.L., X.C. and W.Y. All authors have read and agreed to the published version of the manuscript.

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**Sample Availability:** Samples of the compounds 4a–4t are available from the authors.

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