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Synthesis of Functionalized Indole-1-oxide Derivatives via Cascade Reactions of Allenynes and ^{t}BuONO

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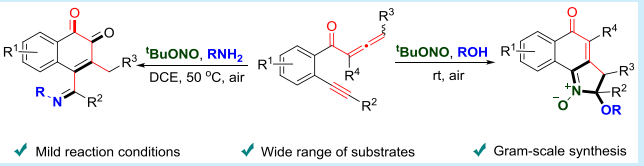
Supporting Information

ABSTRACT: This paper presents a novel access to 5-oxo-2*H*-benzo[*g*]indole-1-oxides/functionalized naphthalene-1,2-diones via the cascade reaction of allenynes with alcohols/amines and ^{t}BuONO without using any catalyst. Mechanistically, the formation of 5-oxo-2*H*-benzo[*g*]indole-1-oxides involves a cascade process combining [2 + 2] cycloaddition, 1,6-addition, and ring expansion of the in situ formed cyclobutene intermediate. The construction of naphthalene-1,2-diones should undergo a ring-opening pathway. Moreover, the utility of benzoindole-1-oxides was demonstrated by their easy conversion into pharmaceutically significant 1*H*-benzo[*g*]indol-5-ol derivatives.



The indole unit is a key block of various natural products, electronic materials, and pharmaceuticals.[1] Among various indole derivatives, indole-1-oxide is present widely in alkaloids possessing powerful biological activities. For example, avrainvillamide and stephacidin B possess a strong inhibitory effect on the growth of testosterone-dependent prostate and breast cancer cell lines.[2] As another example, waikialoid A showed potent inhibition to biofilm formation, thus providing a novel and effective approach to combating refractory infections (Figure 1).[3]

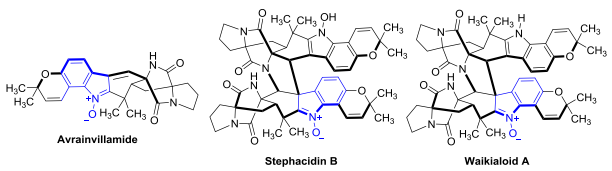
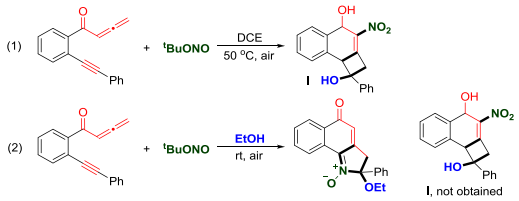


Figure 1. Alkaloids containing the indole-1-oxide moiety.

Due to their importance, a number of methods based on different synthetic strategies have been developed for the synthesis of indole-1-oxide and its derivatives. Traditionally, they were prepared via oxidation of indoles[4] or zinc-promoted intramolecular reductive condensation of 1-(2-nitrophenyl)-2-ones.[2a,d] Most of these reported methods are efficient and reliable, but some of them still suffer from tedious synthetic procedures, unselective oxidation, generation of hazardous wastes, or use of expensive/toxic metal catalysts. Thus, the development of more sustainable and straightforward methods for the construction of indole-1-oxides is urgently needed.

Meanwhile, allene and allene-yne derivatives were found to possess rich and diverse reactivity and have thus been used in the preparation of various kinds of organic compounds.[5,6] From this aspect, a novel method for the synthesis of cyclobutanol-fused 2-nitronaphthalen-1-ols (**I**, Scheme 1, (1)) through tandem reactions of benzene-linked allene-ynes, prepared in three routine steps from commercial 2-bromobenzaldehydes,[5h,6b,7] with ^{t}BuONO (*tert*-butyl nitrite, TBN) using DCE as the reaction medium, has been disclosed by our group.[8] During that study, we serendipitously found that when the above-mentioned reaction was carried out in ethanol instead of DCE, an unexpected cascade reaction occurred to construct an indole-1-oxide derivative (Scheme 1, (2)). Herein, we report the results in detail.

Scheme 1. Varied Reactions of Benzene-Linked Allene-Yne with TBN in Different Solvents



At first, 1-(2-(phenylethynyl)phenyl)buta-2,3-dien-1-one (**1a**) was used as the substrate to react with TBN (**3**, 2 equiv) in ethanol (**2a**, 2 mL) at rt for 3 h, from which the formation of the initially desired cyclobutanol-fused 2-nitronaphthalen-1-ol (**I**) was not observed. Instead, 2-ethoxy-5-oxo-2-phenyl-3,5-dihydro-2*H*-benzo[*g*]indole-1-oxide (**4a**), the structure of

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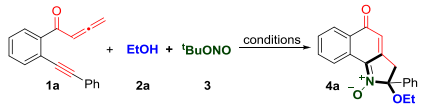
which was confirmed by a single-crystal X-ray diffraction study, was formed in 76% yield (Table 1, entry 1). Notwithstanding

Table 1. Optimization Studies[a]



entry	catalyst	T (°C)	time (h)	yield of **4a** (%)[b]
1[c]		rt	3	76
2		rt	3	80
3[d]		rt	3	75
4[e]		rt	3	80
5[f]		rt	3	41
6	HOAc	rt	3	76
7	TFA	rt	3	65
8	TfOH	rt	3	61
9		50	3	76
10		rt	6	81
11[g]		**rt**	**3**	**82**

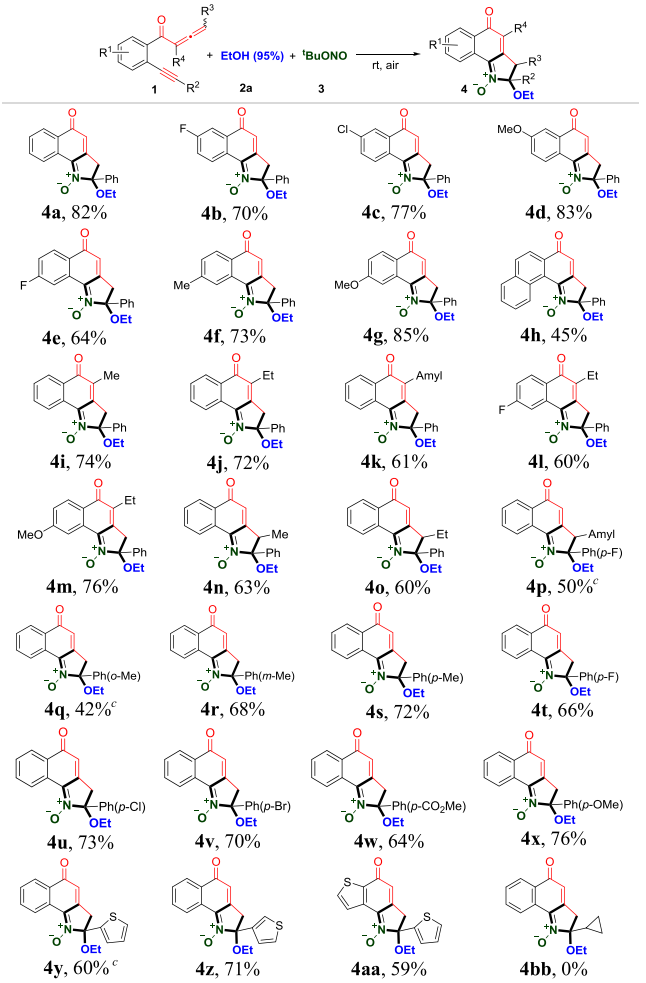
[a]Reaction conditions: **1a** (0.5 mmol), EtOH (10 mmol, 0.6 mL), TBN (1 mmol), rt, air, 3 h. [b]Isolated yield. [c]EtOH (2 mL). [d]EtOH (5 mmol, 0.3 mL). [e]TBN (1.5 mmol). [f]TBN (0.5 mmol). [g]95% EtOH (10 mmol, 0.61 mL) was used.

that compound **I** was not obtained, the construction of **4a** owns two notable features. First, it reveals an unprecedented cascade procedure consisting of formation of a cyclobutene moiety, subsequent radical addition, and ring expansion without a metal catalyst. Second, it gives a synthetically and biologically valuable benzoindole-1-oxide derivative through a straightforward pathway using TBN as an environmentally friendly and cheap NO source.[9]

Encouraged by the above result, a systematic study on this reaction with the aim to develop it into a general method for the preparation of indole-1-oxide derivatives was conducted. First, the loading of EtOH was reduced from 2 to 0.6 mL (10 mmol, 20 equiv) or 0.3 mL (5 mmol, 10 equiv) (Table 1, entries 2 and 3). It turned out that using 0.6 mL (20 equiv) of EtOH as both substrate and solvent could guarantee an effective transformation, giving **4a** in a yield of 80%. Second, increasing or reducing the loading of TBN did not benefit this reaction (entries 4 and 5 vs 2). Third, different acids, such as HOAc, TFA, and TfOH, were tried as possible catalysts. However, no better result was obtained (entries 6–8). Fourth, when the reaction temperature was increased from rt to 50 °C, a slight decrease in the yield of **4a** was observed (entry 9). Further study showed that prolonging the reaction time could not improve the yield of **4a** obviously (entry 10). Finally, we tried to use the less expensive and more sustainable 95% EtOH to replace EtOH as substrate and reaction medium. Under this circumstance, **4a** precipitated upon cooling the resulting reaction mixture to 0 °C and was collected through simple filtration in 82% yield (entry 11).

With the optimized conditions in hand, the reaction scope was subsequently explored by varying the substituents attached on the linking benzene ring of allene-ynes **1**. It was found that whether allene-ynes with electron-withdrawing groups (EWGs), such as fluoro and chloro, or those with electron-donating group (EDG) methoxy were compatible with this reaction and afforded products **4a**–**4g** in 64–85% yields (Scheme 2). Overall, substrates bearing EDGs showed better efficiency

Scheme 2. Scope of Substrates for the Formation of 4 (1)[a,b]



[a]Reaction conditions: **1** (0.5 mmol), EtOH (10 mmol, 95%), TBN (1 mmol), rt, air, 3 h. [b]Isolated yield via precipitation and filtration. [c]Isolated yield via column chromatography.

than those with EWGs (**4d** and **4g** vs **4b**, **4c**, and **4e**). In addition, naphthalene-linked allene-yne could also lead to target product **4h** in 45% yield. Then, to test some more challenging functional groups, we have been trying hard to synthesize substrates with an amine, hydroxyl, or nitro group. However, our efforts in this regard failed. Further study showed that **1** bearing a methyl, ethyl, or amyl group at the internal or terminal position of the allenic unit was suitable to give **4i**–**4p** in 50–76% yields.

In addition, substrates with either EDGs or EWGs on the arylalkynyl moiety worked well and delivered products **4q**–**4x** in 42–76% yields. When the R^2 unit was a 2-thienyl or 3-thienyl group, products **4y** and **4z** were obtained in 60 and 71% yields, respectively. Then, we found that thiophene-tethered allene-yne could also react with EtOH and TBN to afford **4aa** in 59% yield. Nevertheless, a substrate with a cyclopropyl group on the alkynyl moiety failed to give the target product **4bb**.

Next, the suitability of different alcohol substrates (**2**) was investigated by using **1a** as the model substrate. It was first found that alcohols with either a shorter or longer alkyl chain compared with ethanol were compatible to afford **4cc** and **4dd** (Scheme 3). Branched chain alcohol accessed the corresponding product **4ee** in moderate yield. Interestingly, both allyl and propargyl alcohol were compatible with the applied radical

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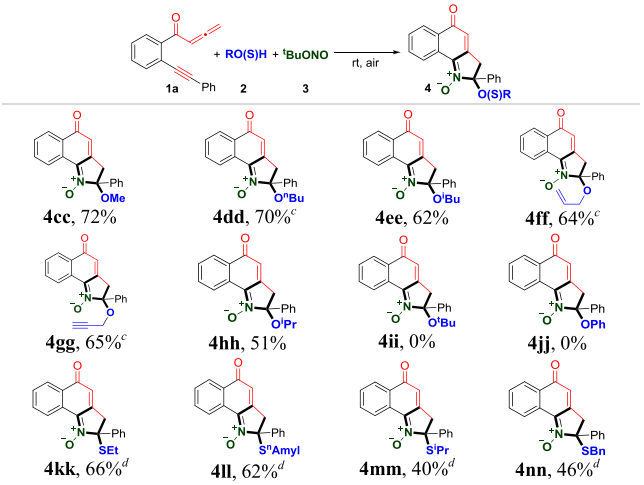
Scheme 3. Scope of Substrates for the Formation of 4 (2)[a,b]

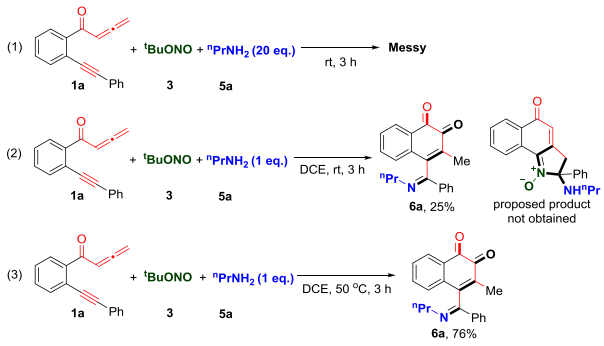


[a]Reaction conditions: **1a** (0.5 mmol), alcohol (10 mmol), TBN (1 mmol), rt, air, 3 h. [b]Isolated yield via precipitation and filtration. [c]Isolated yield via chromatography. [d]Thiol (2.5 mmol), DCE (2 mL), isolated yield via column chromatography.

reaction conditions, thus allowing for possible subsequent structural elaboration of the products (**4ff**, **4gg**). In addition to primary alcohols, secondary alcohol could also take part in this reaction efficiently to give **4hh**. On the other hand, *tert*-butyl alcohol and phenol were unable to convert into the according products (**4ii**, **4jj**), most likely owing to their steric hindrance and/or weak nucleophilic ability. Promisingly, thiols were also suitable for this cascade reaction and produced **4kk**−**4nn** in 40−66% yields.

Thus far, we have established an efficient synthesis of indole-1-oxides from the reactions of allene-ynes with alcohols/thiols and TBN. To further explore the scope of this transformation, propylamine (**5a**) instead of alcohol was subjected to the standard conditions, as shown in Scheme 4, (1). However, the

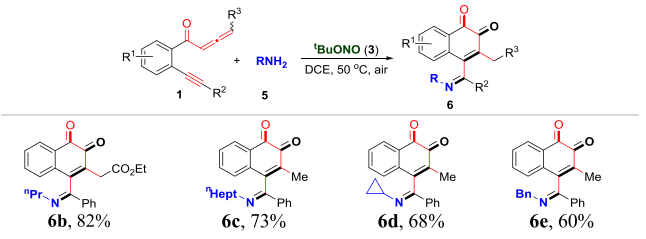
Scheme 4. Formation of 6a



reaction system was messy. Then, the loading of **5a** was decreased to 1 equiv, and DCE was used as the reaction medium to improve the efficiency of this transformation. Surprisingly, an iminated (*Z*)-naphthalene-1,2-dione (**6a**, 25%) was composed without the formation of indole-1-oxide (Scheme 4, (2)). The *Z*-selectivity of **6a** was confirmed by X-ray diffraction analysis. It is known that the naphthalene-1,2-dione scaffold constitutes the core of numerous natural and pharmaceutical compounds.[10] Therefore, the efficient and facile formation of **6a** is synthetically promising. Thus, extensive parameters were screened to improve the formation of **6a**. As a result, when **1a** was treated with TBN (**3**, 2equiv) and **5a** (1equiv) in DCE at 50 °C for 3 h, **6a** was obtained in a maximum yield of 76% (Scheme 4, (3)).

Prompted by the above results, we also used some other allene-ynes to explore the generality of this transformation for the formation of naphthalene-1,2-diones. It showed that all of them were suitable substrates to give **6b**−**6e** in 60−82% yields (Scheme 5).

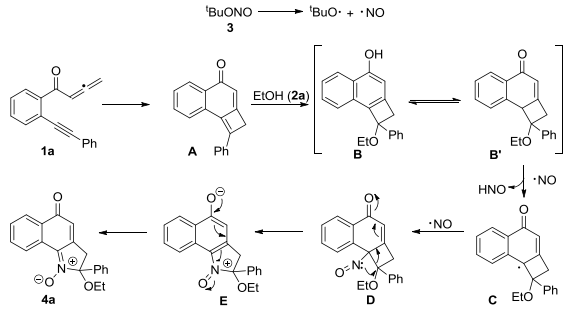
Scheme 5. Scope of Substrates for the Formation of 6[a,b]



[a]Reaction conditions: **1a** (0.5 mmol), **5** (0.5 mmol), TBN (1 mmol), DCE (2 mL), 50 °C, air, 3 h. [b]Isolated yield via column chromatography.

Based on the experimental results and previous reports,[6,11] a putative pathway leading to the formation of **4a** was proposed in Scheme 6. Initially, intramolecular [2 + 2] cycloaddition of **1a**

Scheme 6. Plausible Pathway Accounting for 4a



occurs to afford intermediate **A**.[6] Subsequent 1,6-addition of ethanol to **A** gives intermediate **B**, which then undergoes a tautomerization to form **B′**.[6c] Next, the NO radical (•NO), generated from the decomposition of TBN, extracts a hydrogen from **B′** to deliver a radical intermediate **C**. Subsequently, **C** couples with •NO to give intermediate **D**. Then, **E** was formed via a ring expansion of **D**.[11d] Finally, tautomerization of **E** yields the final product **4a**.

To confirm the proposed pathway, some control experiments were conducted. First, (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) as a radical inhibitor was added to the reaction, and no product was formed, indicating the reaction might involve a radical process (Scheme 7, (1)). Second, treating **1a** with 95% EtOH in the absence of TBN affords the proposed intermediate **B** in 95% yield (Scheme 7, (2)). Next, **B** was subjected to the standard conditions to afford **4a** in 82% yield (Scheme 7, (3)). The above results suggested that **B** might be the key intermediate for the construction of **4a** from **1a**. Third, combination of ^{t}BuOO^{t}Bu (TBP) and Bu_3SnD was used to capture the radical intermediate **C**, from which [D_1]-**B′**/[D_1]-**B** was not obtained (Scheme 7, (4)). It indicated that the hydrogen of intermediate **B′** might be extracted by the in situ

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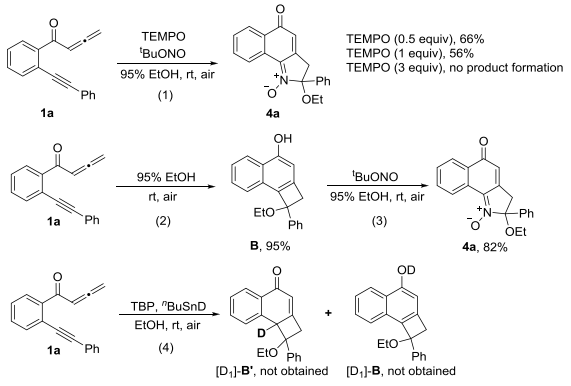
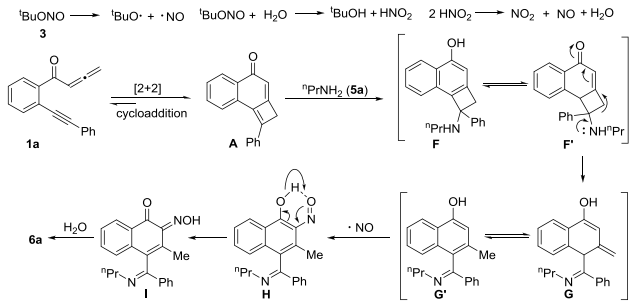
Scheme 7. Control Experiments (I)



generated radical NO rather than radical ^{t}BuO with possible steric hindrance.

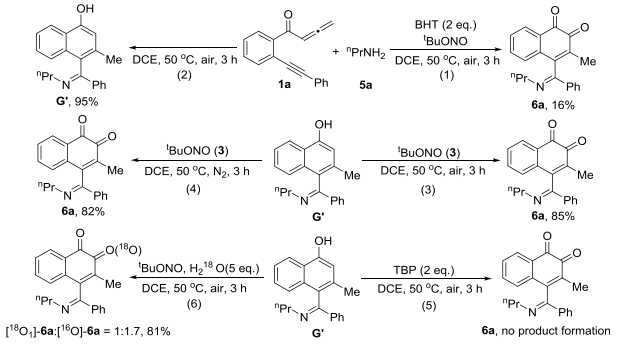
For the construction of **6a**, the initial generation of intermediate **A** should be involved. Subsequent 1,6-addition of amine (**5a**) to **A** delivers intermediate **F**. Then, tautomerization of **F** occurs to afford **F′**, which tends to undergo a ring-opening process and intramolecular hydrogen transfer to form intermediate **G** with unstable exocyclic double bonds. Then, **G** isomerizes into more stable intermediate **G′**.[6d] Next, addition of the in situ generated NO radical[9d] to intermediate **G′** and subsequent hydrogen migration generate oxime intermediate **I**,[12a] which was further hydrolyzed to give the final product **6a** (Scheme 8).[12b]

Scheme 8. Plausible Pathway Accounting for 6a



More control experiments were performed to confirm the mechanism. First, BHT (butylated hydroxytoluene, 2 equiv) was used as a radical inhibitor in this reaction. As a result, the yield of **6a** was decreased to 16% (Scheme 9, (1)). It showed that the

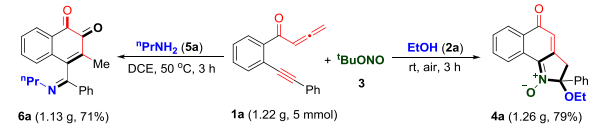
Scheme 9. Control Experiments (II)



construction of **6a** should undergo a radical pathway. Next, **1a** was treated with **5a** in the absence of TBN and afforded iminated (*Z*)-1-naphthol (**G′**) in 95% yield (Scheme 9, (2)). Second, in the absence of **5a**, **G′** was subjected to the standard reaction conditions and delivered **6a** in 85% yield (Scheme 9, (3)), indicating that **G′** may be the intermediate for the formation of **6a**. Subsequently, when the reaction for the transformation of **G′** was carried out under nitrogen instead of air, **6a** was still obtained in 82% yield (Scheme 9, (4)), suggesting that the effect of molecular oxygen might be excluded. Third, treating **G′** with TBP instead of TBN could not deliver the product **6a** (Scheme 9, (5)), excluding the effect of radical ^{t}BuO•. $H_2{}^{18}O$ (5 equiv) was then added in the reaction for the preparation of **6a** from **G′** (Scheme 9, (6)), from which [$^{18}O_1$]-**6a** and [^{16}O]-**6a** were obtained in a ratio of 1:1.7 (see Supporting Information, determined by HRMS analysis). It hints that H_2O should be a source of the oxygen atom of the newly formed carbonyl group embedded in **6a**.

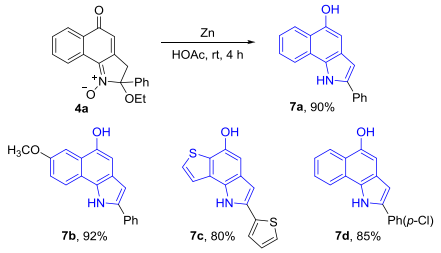
To demonstrate the scalability of the synthetic method developed in this paper, the preparations of **4a** and **6a** were performed at a 5 mmol scale. As a result, **4a** and **6a** were efficiently obtained in 79 and 71% yields, respectively (Scheme 10).

Scheme 10. Gram-Scale Synthesis of 4a and 6a



Having established a convenient and efficient synthesis of benzoindole-1-oxide derivatives (**4**), the synthetic applications of **4** were subsequently studied (Scheme 11). Thus, **4a** was

Scheme 11. Synthesis of 1*H*-Benzo[*g*]indol-5-ols (7)



treated with zinc powder in acetic acid at rt for 4 h. From this reaction, 2-phenyl-1*H*-benzo[*g*]indol-5-ol (**7a**) was obtained in 90% yield. This unprecedented transformation is attractive as benzo[*g*]indol-5-ol is a key building block of many compounds displaying significant medicinal activities.[13] To explore its generality, the suitability of other benzoindole-1-oxides was studied. It was found that all of them could be smoothly transformed into products **7b**−**7d** in high yields, thus providing a highly convenient and efficient pathway toward 1*H*-benzo-[*g*]indol-5-ol derivatives.

In summary, an efficient and novel methodology for the synthesis of 5-oxo-2*H*-benzo[*g*]indole-1-oxides/functionalized naphthalene-1,2-diones via the cascade reaction of allenynes with alcohols/amines and TBN without using any catalyst has been successfully developed in this paper. Notably, most of the reactions used aqueous alcohol as the substrate and involved a

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convenient purification process of simple precipitation and filtration. With advantages such as mild reaction conditions, a wide range of substrates, a simple operational process, and large-scale preparation, this facile method is expected to find more applications in expanding the scaffold space of *N*-oxide and naphthalene-1,2-dione derivatives as valuable candidates and versatile intermediates in medicinal chemistry.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00968.

Experimental procedure, characterization data, and NMR spectra of all products (PDF)

Accession Codes

CCDC 1878661 and 1882514 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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