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Solvent-Regulated Coupling of 2-Alkynylbenzaldehydes with Cyclic Amines: Selective Synthesis of Fused N-Heterocycles and Functionalized Naphthalene Derivatives

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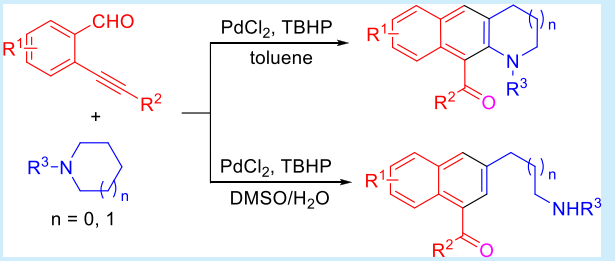
ABSTRACT: An efficient synthesis of 1,2,3,4-tetrahydrobenzo[*g*]-quinoline derivatives through $PdCl_2$-catalyzed, TBHP-promoted, and toluene-mediated dehydrogenation/[4+2] cycloaddition of saturated cyclic amines with 2-alkynylbenzaldehydes was developed. On the contrary, when the reaction medium was changed from toluene to DMSO/H_2O, another class of important compounds, naphthyl chain amines, formed via a dehydrogenation−intermolecular condensation−C−N bond cleavage−intramolecular condensation pathway, was obtained with good selectivity.



Fused N-heterocycles are attracting more attention because of their crucial roles in materials[1] and pharmaceuticals.[2] Due to their unique photochemical or electrochemical properties, some of them have been used as luminescent or semiconductor materials.[1] In addition, fused N-heterocycles are essential building blocks of various bioactive derivatives, which display in vivo potent analgesic activity[2a] or have a significant effect on the treatment of Alzheimer's disease,[2b] SiHa human tumor,[2c] etc. (Figure 1). The direct C(sp^3)−H bond

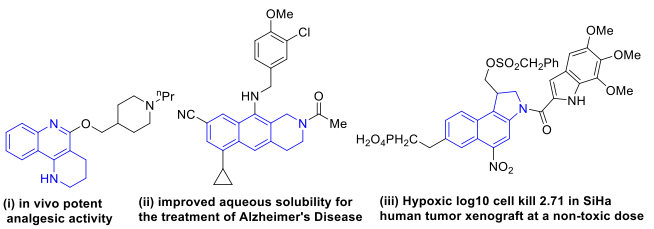


Figure 1. Bioactive molecules containing the fused N-heterocyclic moiety.

functionalization of readily available cyclic amines is an atom-economic and attractive transformation for the synthesis of different kinds of N-heterocyclic compounds. However, a majority of previous discoveries were focused on the single activation of the position α[3] or β[4] to the nitrogen atom. The dual C(sp^3)−H bond functionalization of saturated cyclic amines in a single step, which was considered to be an attractive way to synthesize fused N-heterocyclic derivatives, has rarely been reported.[5]

On the contrary, benzopyryliums, which were formed from the transition metal-catalyzed intramolecular benzannulation of 2-alkynylbenzaldehydes, usually served as appealing 4-π donors to undergo cycloadditions with π-bond units to synthesize polycyclic frameworks.[6−8] For example, Asao, Yamamoto, and co-workers initially discovered efficient methods toward naphthyl ketones or debenzoylated naphthalenes through the $AuCl_3$/Cu(OTf)$_2$-catalyzed benzannulation between 2-alkynylbenzaldehydes and alkynes.[7b,c] Then, the benzannulation of 2-alkynylbenzaldehydes with alkenes, enols, or benzynes to compose different polycyclic compounds was performed in succession.[7d−g] Meanwhile, the groups of Dyker and Patil tested the other olefins/electron-rich heteroarenes and epoxide as partners to react with 2-alkynylbenzaldehydes.[8]

Recently, Liu's group disclosed novel methods for accessing distinct α-carbonylnaphthalenes by Cu(OAc)$_2$-catalyzed cycloaddition of 2-alkynylbenzaldehydes with isoxazoles.[9] Until now, while benzannulation of 2-alkynylbenzaldehydes with various unsaturated hydrocarbons was reported, the cycloaddition between 2-alkynylbenzaldehydes and inactivated cyclic amines with saturated chemical bonds to form fused N-heterocyclic compounds is still unknown. Thus, inspired by the elegant pioneering studies mentioned above and as a continuation of our work on the functionalization of cyclic amines,[10] we herein report a new method for the synthesis of 1,2,3,4-tetrahydrobenzo[*g*]quinoline derivatives through $PdCl_2$-catalyzed dehydrogenation/[4+2] cycloaddition of saturated cyclic amines with 2-alkynylbenzaldehydes (Scheme 1).

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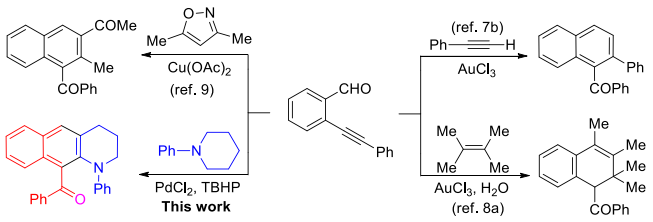
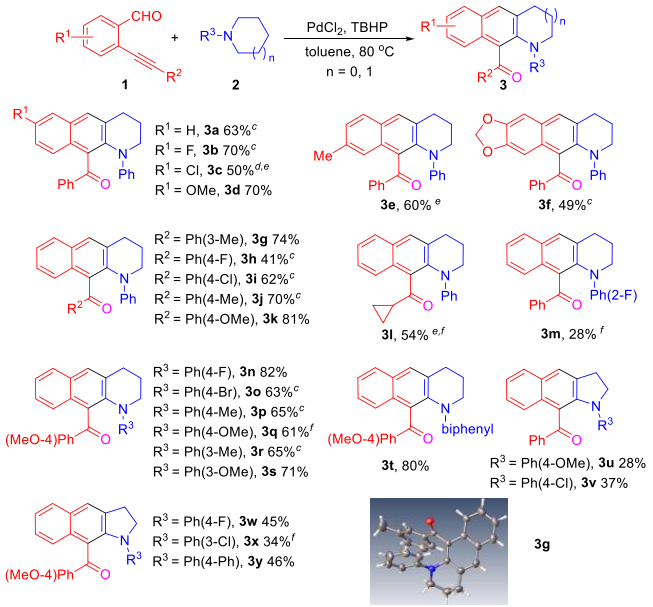
Scheme 1. Previous Work and This Work



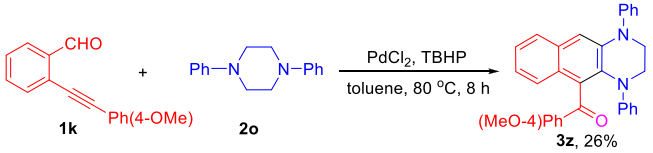
Considering the decomposition of saturated cyclic amines in the oxidant circumstance,[10d,e] 2-(phenylethynyl)benzaldehyde (**1a**, 1 equiv) was initially treated with an excess of 1-phenylpiperidine (**2a**, 3 equiv) in toluene at 80 °C under air for 8 h by using $PdCl_2$ (0.05 equiv) as the catalyst and *tert*-butyl hydroperoxide (TBHP, 1 equiv) as the oxidant, from which phenyl(1-phenyl-1,2,3,4-tetrahydrobenzo[*g*]quinolin-10-yl)methanone (**3a**) was isolated in a yield of 63% (Schemes 2 and 3a). After screening various catalysts and oxidants, we found the combination of $PdCl_2$ and TBHP was the most effective (for details, see Table S1). Subsequently, several solvents were tested. Accordingly, the results showed that polar solvents were more favorable for the selective formation of phenyl{3-[3-(phenylamino)propyl]naphthalen-1-yl}methanone (**4a**), which was formed via a dehydrogenation−intermolecular condensation−C−N bond cleavage−intramolecular condensation pathway. Among them, the DMSO/H_2O solvent (19:1) was optimal to afford **4a** in a yield of 43% (for details, see Table S1). Then, sequentially increasing the loads of $PdCl_2$ and TBHP to 0.1 and 2 equiv, respectively, gave **4a** in the highest yield of 62% (Schemes 4a and 5).

Scheme 2. Substrate Scope for the Synthesis of 3[a,b]

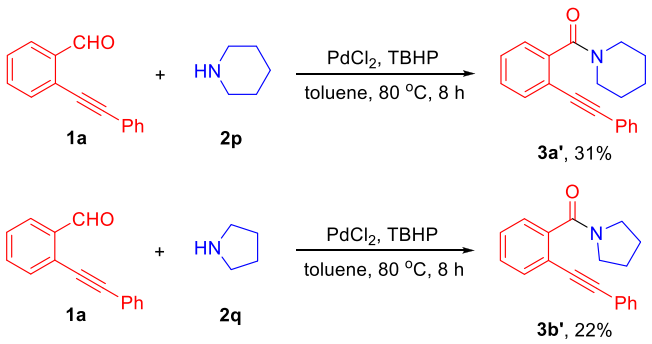


[a]Reaction conditions: 0.2 mmol of **1**, 0.6 mmol of **2**, 0.01 mmol of $PdCl_2$, 0.2 mmol of TBHP, toluene (1 mL), 80 °C, air, 8 h. [b]Isolated yields. [c]Naphthyl chain amine (**4**) was formed in a trace amount. [d]With 0.4 mmol of TBP instead of TBHP. [e]Naphthyl chain amine (**4**) was obtained as a byproduct. [f]The 2-(2-oxo-2-phenylethyl)-benzaldehyde derivative (**5**) was obtained as a byproduct.

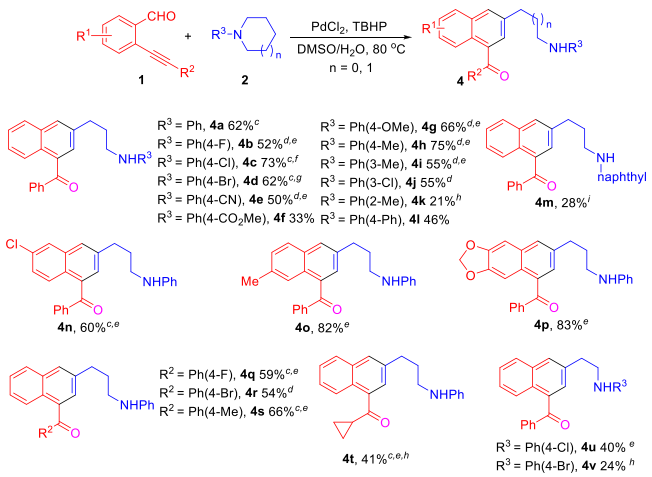
Scheme 3. Synthesis of 3z



Scheme 4. Synthesis of 3a′ and 3b′



Scheme 5. Substrate Scope for the Synthesis of 4[a,b]



[a]Reaction conditions: 0.2 mmol of **1**, 0.6 mmol of **2**, 0.02 mmol of $PdCl_2$, 0.4 mmol of TBHP, DMSO/H_2O (19:1, 1 mL), 80 °C, air, 8 h. [b]Isolated yields. [c]The 1,2,3,4-tetrahydrobenzo[*g*]quinoline derivative (**3**) was obtained as a byproduct. [d]The 1,2,3,4-tetrahydrobenzo-[*g*]quinoline derivative (**3**) was formed in a trace amount. [e]DMSO/H_2O (9:1, 1 mL). [f][1-(4-Chlorophenyl)-1,2,3,4-tetrahydrobenzo[*g*]-quinolin-1-yl](phenyl)methanone (**3aa**) as a byproduct was obtained in a yield of 9%. [g][1-(4-Bromophenyl)-1,2,3,4-tetrahydrobenzo[*g*]-quinolin-1-yl](phenyl)methanone (**3bb**) as a byproduct was obtained in a yield of 10%. [h]The 2-(2-oxo-2-phenylethyl)benzaldehyde derivative (**5**) was obtained as a byproduct. [i]With 0.4 mmol of TBP instead of TBHP and DMSO (1 mL).

Having the optimum reaction conditions in hand, we began to explore the substrate scope of this dual C(sp^3)−H bond functionalization reaction for the preparation of **3**. First, various 2-alkynylbenzaldehydes **1** bearing different functional groups, such as fluoro, chloro, methyl, methoxy, and methylenedioxy groups, on the aryl-aldehyde or aryl-terminal alkyne moiety were tried. It showed that all of them were suitable for this transformation and afforded the corresponding products **3a**−**3k** in yields of 41−81% (Scheme 2). Moreover, the alkyne-tethered benzene rings of **2** with electron-donating groups were

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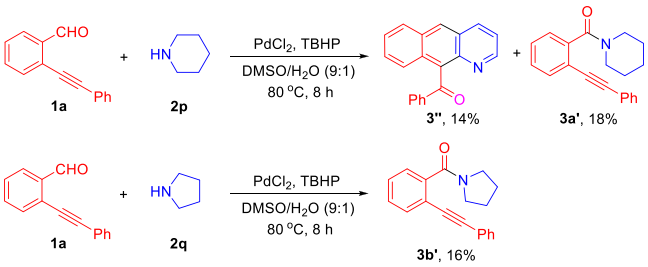
more favorable than those with electron-withdrawing groups (**3g**, **3j**, and **3k** vs **3h** and **3i**). Notably, alkyl-substituted alkyne **1l** took part in this reaction smoothly to give **3l** in a yield of 54%. Second, *N*-aryl piperidines **2** with different substituents attached to the phenyl rings were also tested. Delightfully, functional groups ranging from electron-deficient groups (fluoro and bromo) to electron-rich groups (methyl and methoxy) were suitable to this transformation, delivering target products **3m**−**3s** in yields of 28−82% without showing an obvious electronic effect. However, no intended product was formed when 1-(*o*-tolyl)piperidine was used as the substrate, probably due to the steric effect. In addition, this reaction was compatible with 1-biphenylpiperidine for the production of **3t** in a yield of 80%. Third, the suitability of different *N*-aryl pyrrolidines was explored. It was found that all of them were amenable to this cascade reaction, albeit giving corresponding products **3u**−**3y** in somewhat lower yields. The structure of **3g** was confirmed by X-ray single-crystal diffraction analysis (see the Supporting Information). In addition, byproducts such as naphthyl chain amines (**4**) and/or 2-(2-oxo-2-phenylethyl)benzaldehyde derivatives (**5**) were isolated from some of the reactions for the construction of **3**. The NMR spectra and isolated yields of these byproducts are included in the Supporting Information. Remarkably, besides piperidines, *N*-phenyl pyrazine (**2o**) with two nitrogen atoms could undergo this transformation to furnish **3z** in a yield of 26% (Scheme 3). However, when secondary cyclic amines, such as piperidine and pyrrolidine instead of tertiary amines, were tried, the target 1,2,3,4-tetrahydrobenzo-[*g*]quinoline derivatives were not found, and amide products **3a′** and **3b′** were obtained in yields of 31% and 22%, respectively (Scheme 4).

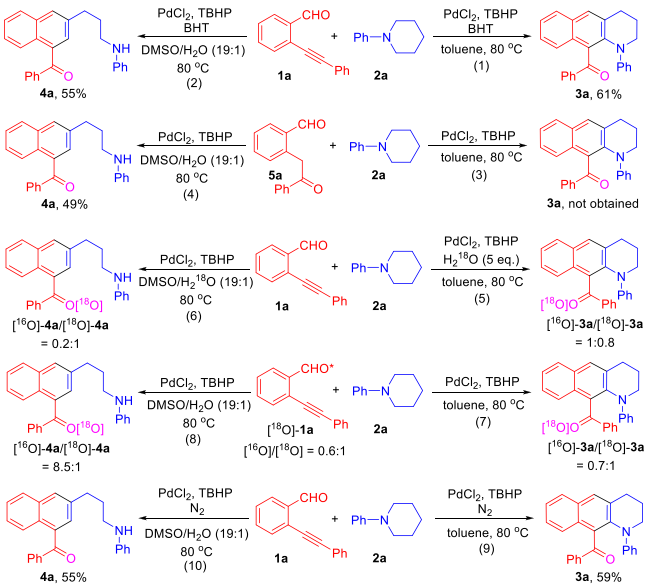
Next, we turned our attention to the substrate scope for the synthesis of **4** (Scheme 5). First, a number of 1-arylpyridines **2** with various substituents, such as fluoro, chloro, bromo, cyano, ester, methoxy, and methyl groups, attached at the *para*, *meta*, or *ortho* position of the phenyl ring were found to be tolerated, giving the desired products **4a**−**4k** in yields of 21−75%. Among them, electron-rich or halogen-substituted *N*-arylpyridines did not affect the efficiency of the reaction obviously (**4b**−**4d**, **4g**, and **4h** vs **4a**), but 1-(4-cyanophenyl)piperidine and 1-[4-(methoxycarbonyl)phenyl]piperidine, which were substituted with strong electron-withdrawing group, gave the desired products (**4e** and **4f**) in somewhat lower yields. Due to steric hindrance, **2** with a methyl unit at the *ortho* position of the phenyl ring transformed into **4k** in a low yield of 21%. Notably, this reaction was compatible with 1-biphenylpiperidine and 1-naphthylpiperidine, delivering **4l** and **4m** in yields of 46% and 28%, respectively. Second, a range of 2-alkynylbenzaldehydes **1** were studied (**4n**−**4s**). The results showed that forms of **1** with electron-rich groups on the phenyl rings were more favorable than those with electron-deficient groups (**4o** and **4p** vs **4n**). Moreover, **1l**, attached with an alkyl-substituted alkyne unit, was suitable for this reaction to afford **4t** in a yield of 41%. Third, 1-aryl-substituted pyrrolidines were tested in this transformation, affording products **4u** and **4v** in yields of 40% and 24%, respectively. In addition, byproducts such as 1,2,3,4-tetrahydrobenzo[*g*]quinoline derivatives (**3**) and/or 2-(2-oxo-2-phenylethyl)benzaldehyde derivatives (**5**) were isolated from some of the reactions for the construction of **4**. The NMR spectra and isolated yields of these byproducts are included in the Supporting Information. Interestingly, when piperidine was used as the substrate, fused N-heterocycle benzo[*g*]quinolin-10-yl(phenyl)methanone (**3″**) and **3a′** were delivered in yields of 14% and 18%, respectively, but pyrrolidine afforded **3b′** in a yield of 16% (Scheme 6).

Scheme 6. Synthesis of 3a′, 3b′, and 3″



To elucidate the reaction pathway, a series of control experiments were conducted. First, 2 equiv of radical inhibitor butylated hydroxytoluene (BHT) was added to the standard reaction systems for the preparation of **3a** and **4a**. It turned out that the yields of **3a** and **4a** were not affected obviously, excluding the radical mechanism [Scheme 7, (1) and (2)].

Scheme 7. Control Experiments



Second, 2-(2-oxo-2-phenylethyl)benzaldehyde (**5a**), which could be isolated from the reaction mixture for the formation of **4a**, was treated with **1a** under the standard conditions for the construction of **3a** and **4a**. Consequently, **3a** was not obtained and **4a** was delivered in a yield of 49%. It showed that **5** may be the possible intermediate for **4a** but not for **3a** [Scheme 7, (3) and (4)]. Third, ^{18}O labeling experiments with $H_2{}^{18}O$ for the formation of **3a** and **4a** were carried out [Scheme 7, (5) and (6)], from which [^{16}O]-**3a** versus [^{18}O]-**3a** and [^{16}O]-**4a** versus [^{18}O]-**4a** were given in a ratio of 1:0.8 and 0.2:1, respectively, as determined by HRMS analysis. Fourth, the reactions with [^{18}O]-**1a** (0.6:1 ^{16}O:^{18}O) were also tested. As a result, the corresponding products [^{16}O]-**3a** versus [^{18}O]-**3a** and [^{16}O]-**4a** versus [^{18}O]-**4a** were obtained in ratios of 0.7:1 and 8.5:1, respectively [Scheme 7, (7) and (8)]. Fifth, when the reactions for the synthesis of **3a** and **4a** were conducted under N_2 instead of air, **3a** and **4a** were still obtained in yields of 59% and 55%, respectively [Scheme 7, (9) and (10)]. Given that H_2O might be

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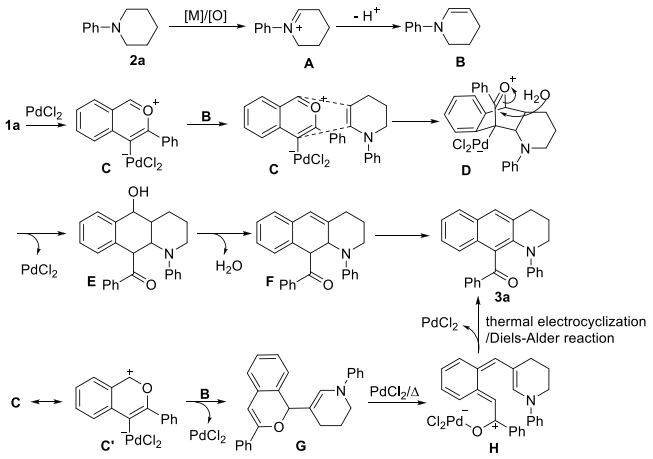
released from these transformations, the results presented above suggested that the oxygen atom of the carbonyl moiety embedded in **4a** might mainly come from H_2O. In addition, both H_2O and **1a** might provide the oxygen source for the formation of **3a** (for details, see the Supporting Information).

On the basis of the experimental results mentioned above and previous reports,[9,10] two possible pathways for the formation of **3a** are proposed in Scheme 8. Initially, **2a** undergoes oxidation

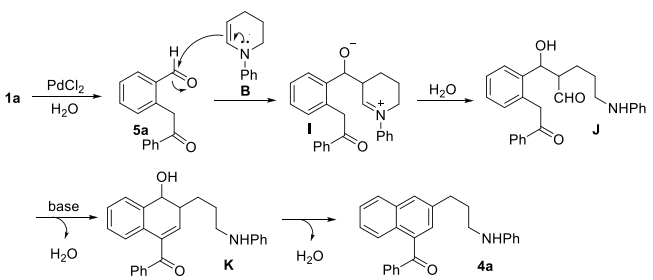
Scheme 8. Proposed Mechanism Accounting for the Formation of 3a



and subsequent dehydrogenation to produce enamine **B**.[10a] Next, [4+2] cycloaddition between Pd-containing benzopyrylium **C** and species **B** occurs to deliver intermediate **D**. Then, **D** is hydrolyzed to give intermediate **E** with the loss of $PdCl_2$, which is attached to benzopyrylium.[9] Subsequently, dehydration and aromatization of **E** successively take place to afford **3a**.[10c] Additionally, when the reaction for the formation of **3a** was conducted under the standard conditions for 4 h, intermediates **E** (calcd, 384.1958; found, 384.1954) and **F** (calcd, 366.1852; found, 366.1852) were detected by HRMS analysis (for details, see the Supporting Information), which might be considered as positive evidence in supporting the mechanism deduced above. For another pathway, enamine **B** reacts with **C′**, which is the resonance form of **C**, to deliver intermediate **G**.[6c] In the presence of $PdCl_2$, **G** undergoes a ring-opening reaction to afford intermediate **H**.[6c] Then, a thermal electrocyclization or Diels–Alder reaction of **H** occurs to give **3a**.[6c]

With respect to the formation of **4a**, the possible pathway is shown in Scheme 9. First, **1a** is hydrolyzed to generate **5a**, which is likely to be obtained in a polar solvent.[11] Then, the aldehyde unit of **5a** reacted with in situ-formed enamine **B** to give iminium

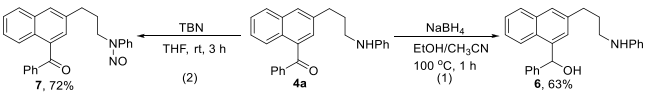
Scheme 9. Proposed Mechanism Accounting for the Formation of 4a



I,[10b] which is hydrolyzed to provide intermediate **J** upon cleavage of the C–N bond.[10f] Next, the intramolecular aldol condensation of **J** occurs to produce intermediate **K**, which undergoes further dehydration to deliver product **4a**.[10c] Notably, when the reaction for the synthesis of **4a** was conducted under the standard conditions for 4 h, intermediates **J** (calcd, 424.1883; found, 424.1894) and **K** (calcd, 384.1958; found, 384.1945) were detected by HRMS analysis (for details, see the Supporting Information), which further confirms the probability of the mechanism mentioned above for the formation of **4a**.

Finally, we explored the applications of the product obtained above. It showed that the carbonyl group in **4a** could be conveniently transformed into hydroxyl unit (**6**, 63%) by subjecting it to $NaBH_4$ in $EtOH/CH_3CN$ at 100 °C for 1 h [Scheme 10, (1)]. Next, considering the easy conversion of

Scheme 10. Synthesis of 6 and 7 from 4a



secondary amines to *N*-nitroso derivatives, which is attracting more attention due to their unique mutagenic properties,[12] **4a** was treated with TBN in THF at room temperature for 3 h to deliver *N*-nitroso compound **7** in a yield of 72% [Scheme 10, (2)].

In conclusion, we have developed a convenient cascade reaction of 2-alkynylbenzaldehydes with saturated cyclic amines to realize the selective synthesis of 1,2,3,4-tetrahydrobenzo[*g*]-quinoline derivatives and naphthyl chain amines mediated by different solvents. Various synthetically useful carbonyl-containing naphthalene derivatives were conveniently obtained from these transformations. Moreover, the diverse reactivity of the carbonyl and amine moieties embedded on the product was demonstrated by the preparation of alcohol and *N*-nitroso derivatives. Further studies of the discovery of new strategies for facile functionalization of cyclic amines are ongoing in our lab.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03442.

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

FAIR data, including the primary NMR FID files, for compounds **3a–3bb**, **4a–4v**, **5a–5c**, **6**, 7, and **I** (ZIP)

Accession Codes

CCDC 2018736 contains 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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