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One-Pot Assembly of 3-Hydroxycarbazoles via Uninterrupted Propargylation/Hydroxylative Benzannulation Reactions

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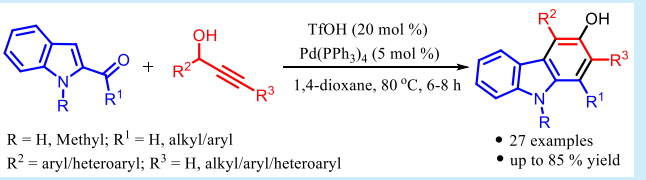
ABSTRACT: A novel strategy for the synthesis of 3-hydroxycarbazoles involving the consecutive propargylation/palladium-catalyzed hydroxylative benzannulation of indole-2-carbonyls with propargylic alcohols has been exploited. This one-pot procedure leads to a wide range of substituted 3-hydroxycarbazoles in high yield with a broad substrate scope. The method was further extended to access furano-carbazole derivatives from dialkynols via tandem annulations.



Carbazoles exemplify a class of privileged scaffolds as valued pharmacophores in pharmaceutical chemistry and leading building blocks in organic synthesis.[1,2] Additionally, they also have found wide applications in photophysical materials such as organic light-emitting devices (OLEDs).[3] In particular, 3-hydroxycarbazole is a ubiquitous structural motif present in numerous bioactive natural products as well as in medicinally important agents (Figure 1).[4] The wide range of applications makes these important frameworks an attractive synthetic target, and many efforts have been devoted to their construction.[5]

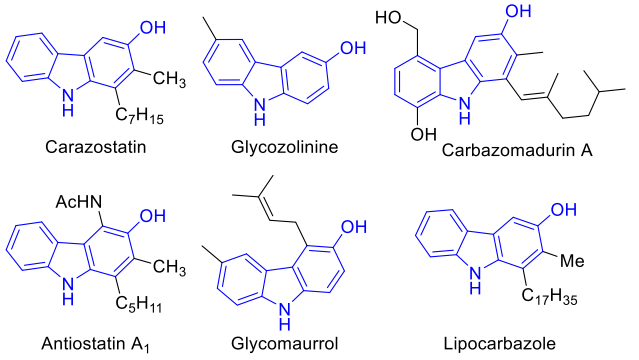
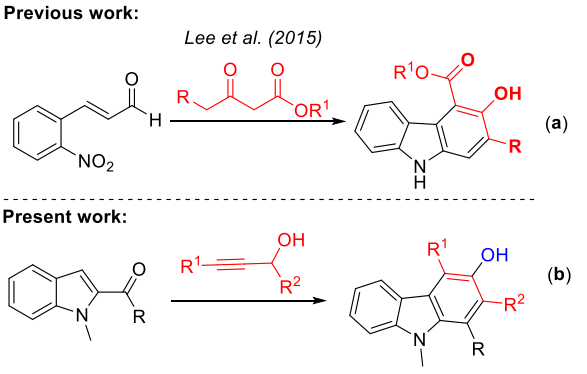


Figure 1. Selected natural products having a 3-hydroxycarbazole framework.

Usually, 3-hydroxycarbazoles are constructed using alkoxy-substituted precursors by the dealkylation reaction to generate the desired hydroxyl group.[5] Knölker and coworkers have developed an iron-mediated method toward the synthesis of various carbazole natural products including 3-hydroxycarbazoles.[1c,6] Alternatively, a few cyclization reactions have also been reported involving carbonylated indole substrates, wherein carbonyl functionality is the source of the hydroxyl group to access 3-hydroxycarbazoles.[7] The preparation of prefunctionalized alkoxy or carbonylated starting materials is tedious because it involves a greater number of steps than commercially accessible sources. Intermolecular annulations for the synthesis of 3-hydroxycarbazoles remain to be less explored.[8] For instance, Lee and Poudel developed base-promoted condensations of 2-nitrocinnamaldehyde or 2-nitrochalcones with β-ketoesters or 1,3-diaryl-2-propanones (Scheme 1a).[8a] In most of these methods, either the carbonyl or the alkoxy group is the source to generate the 3-hydroxy functionality. A versatile one-pot intermolecular reaction to

Scheme 1. Intermolecular Annulations for the Direct Synthesis of 3-Hydroxycarbazoles



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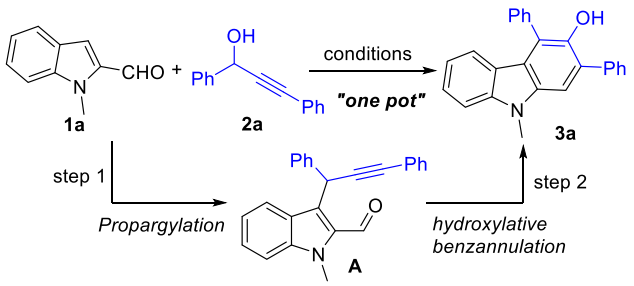
provide diversely substituted 3-hydroxycarbazoles from readily accessible starting materials is of great importance.

On the contrary, propargylic alcohols have extensively served as suitable substrates with a wide range of electrophiles and nucleophiles in the synthesis of numerous heterocyclic and carbocyclic compounds in recent years.[9] In a continuation of our work using 1-arylpropargylic alcohols,[10] herein we wish to report a novel one-pot [3 + 3] annulation of indole-2-carbonyls with 1-aryl propargylic alcohols for the synthesis of corresponding 3-hydroxycarbazoles via uninterrupted sequence involving propargylation and hydroxylative benzannulation reactions (Scheme 1b). To the best of our knowledge, a strategy that installs the hydroxyl group externally at the third position on the carbazole during the annulation (hydroxylative benzannulation) has not been reported to date.

The study began by an unforeseen formation of 3-hydroxycarbazole **3a** in 38% yield from the reaction of **1a** with **2a** and phenylboronic acid in the presence of $Pd(PPh_3)_4$/TfOH in DMF. Because no arylation on the alkyne was observed, the same reaction in the absence of the phenylboronic acid was tested, which gave an identical result (Table 1, entry 1). Because the witnessed reaction provides a product **3a** in 80% yield (Table 1, entry 4). In the absence of a palladium catalyst, the reaction provided the intermediate in 92% yield (Table 1, entry 5), whereas in the absence of TfOH, no reaction took place (Table 1, entry 6). The efficiency of other acid catalysts, such as *p*TSA, $In(OTf)_3$, and $FeCl_3$, was also investigated in a one-pot reaction, and in all of the cases, propargylated intermediate **A** was isolated (Table 1, entries 7–9). Other palladium catalysts $Pd(OAc)_2$ and $PdCl_2$ in the presence of 10 mol % PPh_3 provided a low yield of the product **3a** (Table 1, entries 10 and 11). Furthermore, it was also observed that the addition of an acid and the palladium catalyst together resulted in a low yield (64%) of the product **3a** (Table 1, entry 12). The structure of **3a** was also confirmed by single-crystal X-ray analysis (Figure 2).

Table 1. Optimization of Reaction Conditions[a]



entry	reaction conditions [acid (20 mol %), palladium (5 mol %)]	product	yield (%)[b]
1	TfOH, $Pd(PPh_3)_4$, DMF	**3a**	41
2	TfOH, $Pd(PPh_3)_4$, THF	**A**	52
3	TfOH, $Pd(PPh_3)_4$, CH_3CN	**3a**	34
4	TfOH, $Pd(PPh_3)_4$, dioxane	**3a**	80
5	TfOH, dioxane	**A**	92
6	$Pd(PPh_3)_4$, dioxane		
7	*p*TSA, $Pd(PPh_3)_4$, dioxane	**A**	76
8	$In(OTf)_3$, $Pd(PPh_3)_4$, dioxane	**A**	91
9	$FeCl_3$, $Pd(PPh_3)_4$, dioxane	**A**	73
10	TfOH, $Pd(OAc)_2$ PPh_3, dioxane	**3a**	32
11	TfOH, $PdCl_2$, PPh_3, dioxane	**3a**	27
12[c]	TfOH, $Pd(PPh_3)_4$, dioxane	**3a**	64

[a]Unless otherwise stated, all of the reactions were performed using 0.5 mmol of **1a** with 0.5 mmol of **2a** in 3 mL of solvent and 20 mol % of acid. After stirring at rt for 30 min, 5 mol % of palladium catalyst was added, and the reaction was continued at 80 °C for 7 h. [b]Isolated yield. [c]TfOH and palladium catalyst were added together.

conceptually divergent method to access 3-hydroxycarbazoles, which constitutes a key structural motif in bioactive molecules, we explored this reaction in more detail to optimize the reaction conditions. Thus a reaction of **1a** with **2a** was carried out in one pot by the sequential addition of TfOH (20 mol %) and $Pd(PPh_3)_4$ (5 mol %) in THF, which provided only intermediate **A** in 52% yield (Table 1, entry 2). Switching the solvent to CH_3CN gave the carbazole **3a** in 34% yield (Table 1, entry 3). To our delight, the use of dioxane provided the

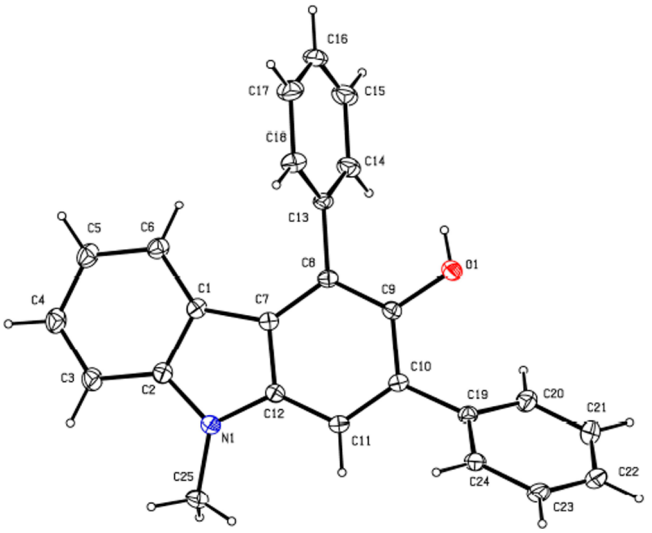
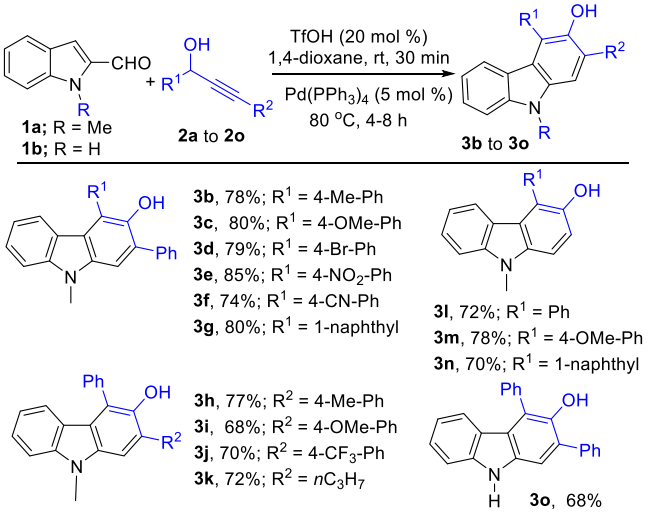


Figure 2. View of **3a**, showing the atom-labeling scheme. Displacement ellipsoids are drawn at the 30% probability level, and H atoms are represented by circles of arbitrary radii. CCDC number 1971748.

Having the optimized reaction condition, the generality of this novel strategy was initially examined by the reaction of indole-2-carboxaldehyde (**1a**) with different propargylic alcohols (Scheme 2). A wide variety of 1-phenyl propargylic

Scheme 2. Scope of Propargylic Alcohols



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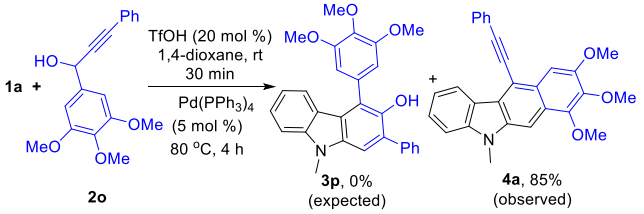
alcohols (see the Supporting Information for the structures of propargylic alcohols), with either electron-donating groups on the aryl ring, such as Me and OMe (**2b** and **2c**), or electron-withdrawing groups, such as Br, NO_2, and CN (**2d**–**f**) substituents and 1-(naphthalen-1-yl)-3-phenylprop-2-yn-1-ol (**2g**), were well endured in [3 + 3] annulation with indole **1a** to give the corresponding carbazoles **3b**–**g** in good to high yield. Similarly, propargylic alcohols having aryl (**2h**–**j**) or alkyl (**2k**) groups tethered to the alkyne were also proved to be suitable for the present one-pot reaction to deliver the 3-hydroxycarbazoles **3h**–**k** in good yield. 1-Arylpropargylic alcohols with terminal alkynes **2l**–**n** functioned well in this consecutive propargylation/hydroxylative benzannulation with **1a** to afford the desired carbazoles **3l**–**n**. Notably, 1*H*-indole-2-carbaldehyde (**1b**) was also well tolerated to react with **2a** to produce 68% of the corresponding product **3o**.

However, propargylic alcohols with highly electron-rich groups at C_1, such as 3,4,5-trimethoxyphenyl (**2o**), failed to offer the desired carbazole **3p**, and, instead, alkynylated-fused carbazole **4a** was isolated in 85% yield (Scheme 3). This might be due to the high nucleophilic reactivity of the electron-rich ring with the aldehyde followed by aromatization.

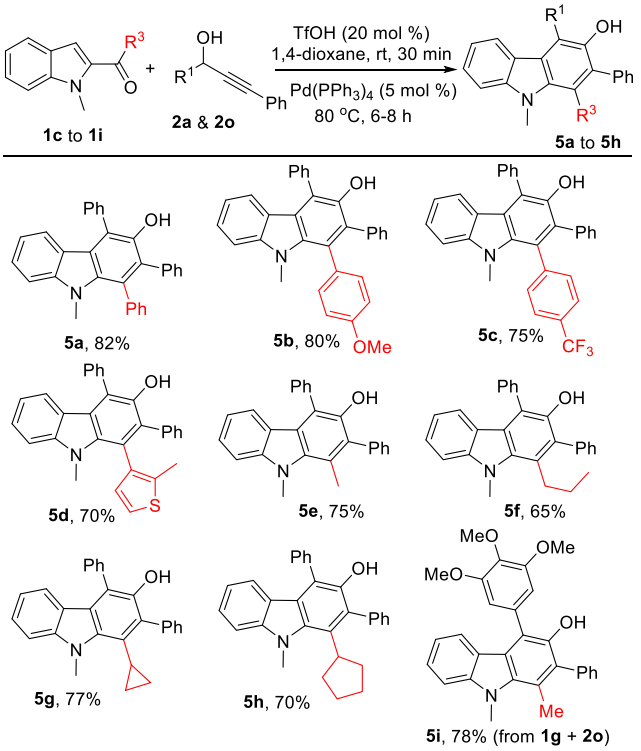
Scheme 3. Reaction of 1a with 2o



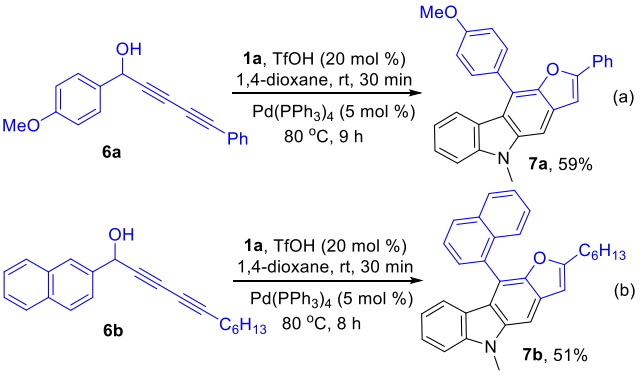
We next turned our interest to studying the scope of the indole-2-carbonyl constituent of the reaction. As shown in Scheme 4, a series of 1-methylindolyl-2-ketones underwent the sequential propargylation/palladium-catalyzed hydroxylative benzannulation with 1,3-diphenylprop-2-yn-1-ol (**2a**) under the present operational conditions, affording the targeted 3-hydroxycarbazoles **5** in high yield. 2-Indolyl phenyl ketone **1c** and aryl ketones bearing an electron-donating (OMe, **1d**) or an electron-withdrawing group (CF_3, **1e**) on the phenyl ring led to the corresponding carbazoles **5a**–**c** in good yield. Additionally, indolyl-2-ketone with heteroaryl (**1f**) was also a suitable partner for this annulation and delivered the product **5d** in 70% yield. Moreover, methyl (**1g**), *n*-propyl (**1h**), cyclopropyl (**1i**), and cyclopentyl (**1j**) indoloyl-2-ketones offered the desired 3-hydroxycarbazoles **5e**–**h** in acceptable yield. The reaction of 2-acetylindole with 1-trimethoxyphenyl propargylic alcohol (**2o**) provided the corresponding carbazole **5i** in 78% yield.

Next, the feasibility of the developed one-pot annulation process with 2,4-diyn-1-oles was investigated. It was predicted that the generated hydroxycarbazole would undergo another cyclization (furan formation) to provide furanocarbazole, a key structural framework present in bioactive natural products and compounds used for OLEDs.[11] Interestingly, the reaction of 1-(4-methoxyphenyl)-5-phenylpenta-2,4-diyn-1-ol **6a** with **1a** gave the envisaged furanocarbazole **7a** in 59% yield (Scheme 5a), involving uninterrupted propargylation, hydroxy-benzannulation, and furan formation (two C–C and two C–O bond-forming reactions). Likewise, furanocarbazole **7b** (51%) was

Scheme 4. Scope of 2-Acylindole



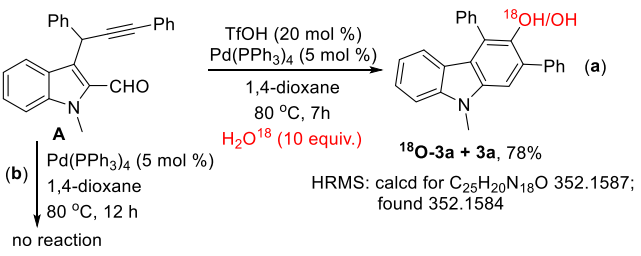
Scheme 5. One-Pot Synthesis of Furanocarbazoles



efficiently obtained from the respective 2,4-diyn-1-ol **6b**, generated from 1-naphthaldehyde (Scheme 5b).

To understand the source of the hydroxyl group, intermediate **A** was treated under optimized reaction conditions by adding ^{18}O-labeled H_2O, which provided the mixture of ^{18}O-incorporated products **^{18}O-3a** and **3a** (Scheme 6a). This supports the source of hydroxyl group as H_2O. The treatment of 3-propargylated indole **A** with 5 mol % of

Scheme 6. Control Experiments



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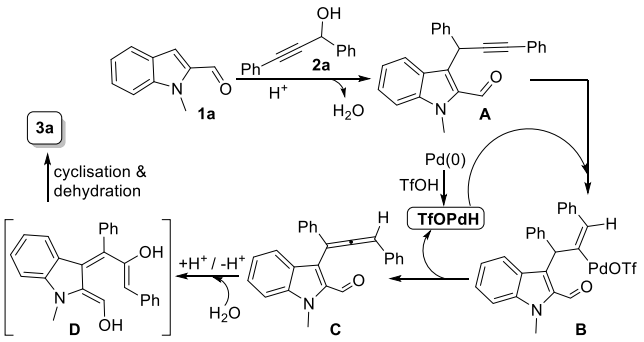
$Pd(PPh_3)_4$ in the absence of TfOH was found to be ineffective, which suggests that TfOH is also required for the hydroxylative benzannulation step.

According to these experimental results and the previous reports, a plausible reaction mechanism is proposed.[12] As shown in Scheme 7, initially, **1a** undergoes the propargylation

Scheme 7. Proposed Mechanism



with **2a** in the presence of TfOH to give intermediate **A**. In the presence of in-situ-generated Pd(II), intermediate **A** undergoes hydropalladation to produce vinylpalladium complex **B**, which upon β-elimination transforms to allene **C**. The hydration of **C** in the presence of acid is expected to give **D**, and subsequent cyclization followed by dehydration leads to the desired product **3a**. Nonetheless, the precise mechanism of the reaction remained indistinct.

In conclusion, the synthesis of 3-hydroxycarbazoles by one-pot consecutive reactions of propargylic alcohols with indole-2-carbonyls has been established, involving palladium-catalyzed hydroxylative benzannulation as the key step. The developed protocol provides access to important diversely substituted 3-hydroxycarbazoles in good to excellent yield. The method was further extended to use 2,4-diyn-1-ols in the reaction, which favored another cyclization to obtain the diannulated products, furanocarbazoles. A broad substrate scope and mild reaction conditions are the attractive features that make the present method valuable.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b04472.

Experimental procedures, characterization details, and ^1H and ^{13}C NMR spectra of new compounds (PDF)

Accession Codes

CCDC 1971748 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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