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Copper-Catalyzed Successive C-C bond formations on Indoles or Pyrrole: A Convergent Synthesis of Symmetric and Unsymmetric Hydroxyl Substituted *N*-H Carbazoles

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Abstract. A novel copper-catalyzed successive C-C bond formations on indoles and pyrrole approach for the direct synthesis of hydroxyl substituted *N*-H carbazoles is described. The current process represents an atom-economical method for the preparation of both symmetric and unsymmetric densely substituted and hydroxyl containing *N*-H carbazoles from easily accessible starting materials without the need for expensive metals and harsh reaction conditions.

Keywords: hydroxyl substituted *N*-H carbazoles; C-C bond formation; copper; indoles; pyrrole

Carbazole and its derivatives are important types of nitrogen containing heterocyclic compounds that play a significant role in both chemistry and biology.[1] For example, numerous molecules, containing the carbzole motif, have shown considerable pharmacological activities such as antiviral, antimalarial, antiestrogenic and antitumor properties.[2] Beside this, cabazoles are also widely used in various organic photoelectronic materials and chromophores due to their structural rigidity and extensive π-conjugation.[3] Consequently, considerable effort has been devoted by the synthetic organic chemistry community to the development of practical and convenient methods for the efficient preparation of functionalized carbazoles during the past several decades.[4]

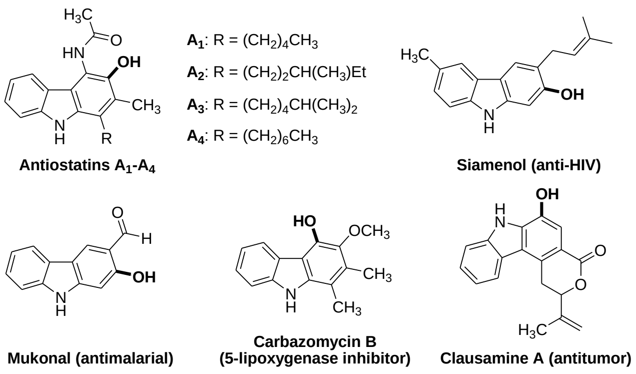
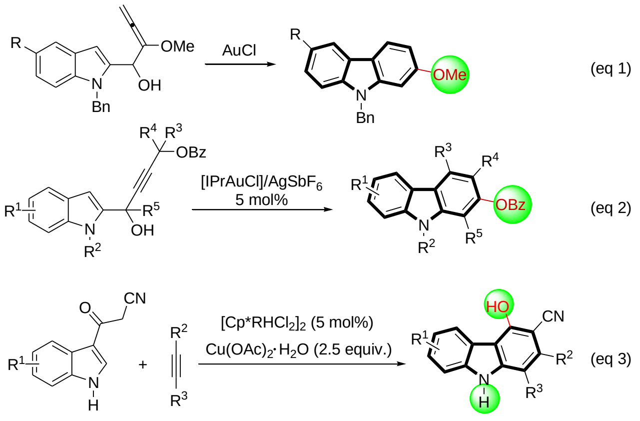
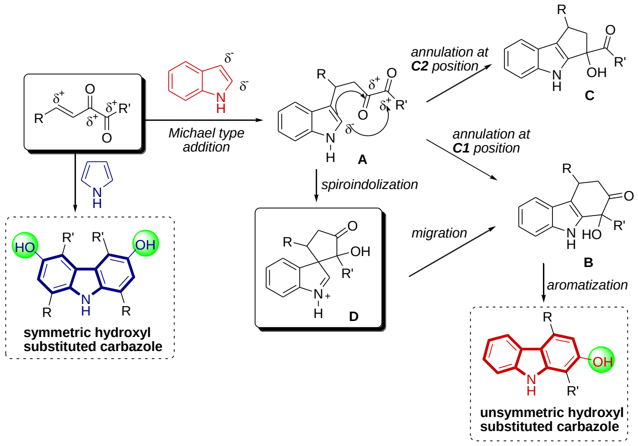


Figure 1. Some representative naturally occurring bioactive hydroxyl substituted *N*-H carbazoles.

Hydroxyl substituted *N*-H carbazoles are a common structural motif present in many biologically active carbazole natural products (Figure 1). Although there are a large number of methods for the synthesis of the carbazole scaffold, the reports for direct preparation of hydroxyl substituted *N*-H carbazoles are quite limited.[5] Indole-to-carbazole transformation represents one of concise methods for carbazole constructions, offering convenient opportunities to obtain the desired functionalized carbazole derivatives.[6] For instance, Ma and co-workers have developed a AuCl-catalyzed benzannulation reaction of 1-indoyl-2,3-allenols for the synthesis of methoxyl substituted carbazoles in 2011 (Scheme 1, eq 1).[7] Subsequently, the same group has also reported an unexpected gold-catalyzed reaction for the synthesis of polysubstituted 2-oxygenated carbazoles from 4-benzoxyl-1-(indol-2-yl)-2-alkynols (Scheme 1, eq 2).[8] More recently, Wang and co-workers discovered a Rh(III)-catalyzed C2 C–H/alkyne annulation reaction of 3-(1H-indol-3-yl)-3-oxopropanenitriles to access hydroxyl substituted *N*-H carbazoles for the first time (Scheme 1, eq 3).[9] However, the use of the above-mentioned poorly available substrates and the operation of deprotection have restricted applications of these reactions. Moreover, the direct synthesis of both symmetric and unsymmetric carbazoles is still relatively underdeveloped. Therefore, the development of efficient methodologies with atom economy starting from easily obtainable substrates to give both symmetric and unsymmetric carbazoles bearing an unprotected *N*H unit as well as a hydroxyl group is still highly desirable.

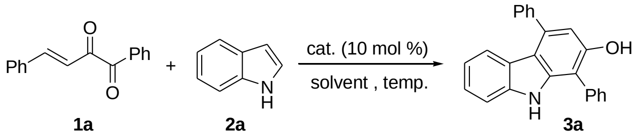


Scheme 1. Synthesis of oxygenated carbazoles.



Scheme 2. Our strategy for the construction of the symmetric and unsymmetric hydroxyl substituted *N*-H carbazoles.

Table 1. Optimization of reaction conditions.[a]



Entry	Catalyst	Solvent	T (ºC)	*t* (h)	Yield (%)[b]
1	$Cu(OTf)_2$	THF	70	2.5	69
2	$Zn(OTf)_2$	THF	70	2.5	48
3	AgOTf	THF	70	2.5	34
4	$Sc(OTf)_3$	THF	70	4.0	trace
5	$Y(OTf)_3$	THF	70	4.0	trace
6	$CuCl_2$	THF	70	2.5	30
7	$CuSO_4$	THF	70	2.5	15
8	$Cu(OTf)_2$	1,4-dioxane	70	2.5	79
9	$Cu(OTf)_2$	$PhCH_3$	70	2.5	63
10	$Cu(OTf)_2$	$Cl(CH_2)_2Cl$	70	2.5	31
11	$Cu(OTf)_2$	CH_3CN	70	2.5	trace
12	$Cu(OTf)_2$	CH_3NO_2	70	2.5	10
13	$Cu(OTf)_2$	1,4-dioxane	40	2.5	32
14	$Cu(OTf)_2$	1,4-dioxane	80	2.5	88
15	$Cu(OTf)_2$	1,4-dioxane	100	2.5	68

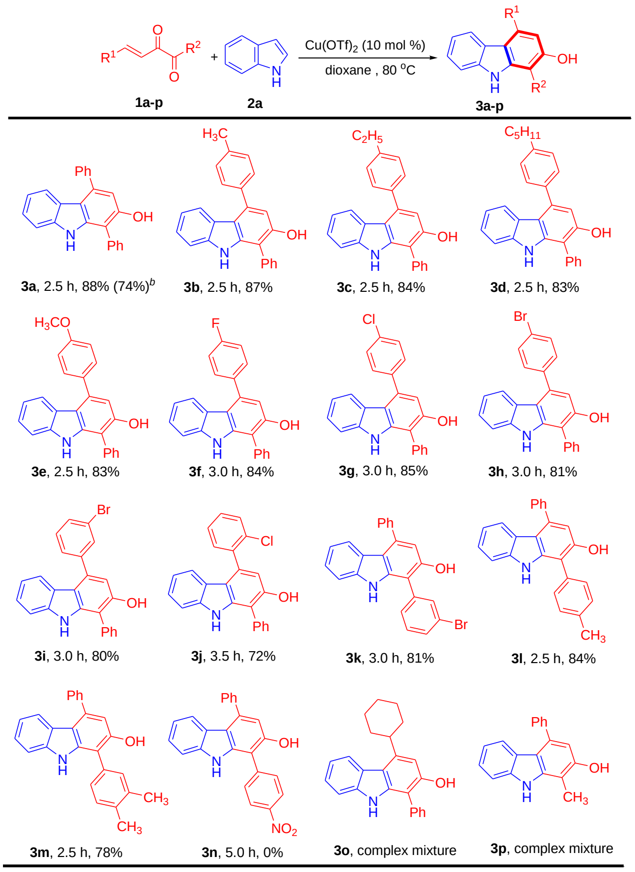
[a] Reaction conditions: **1a** (0.45 mmol), **2a** (0.3 mmol) and catalyst (0.03 mmol) in 4.0 mL of solvent at indicated temperature.

[b] Yield of isolated product after chromatography.

Recently, we became interested in the synthesis and exploring the reactivity of 1,2-dicarbonyl-3-enes, especially toward heterocyclic ring formation.[10] Inspired by these results, we envisage whether that indole without any substituents at C2 and C3 positions could undergo electrophilic attack twice in tandem when a suitable dielectrophile is employed. Obviously, the 1,2-dicarbonyl-3-ene is an ideal dielectrophile. Our original hypothesis is shown in Scheme 2. First, the Michael type addition reaction occurred at one electrophilic site (C4) of the 1,2-dicarbonyl-3-ene, leading to the alkylated product **A** on the C3 position of indole. Subsequently, the C2 position of indole attacks another electrophilic site (C1 or C2) through an intramolecular manner, affording the cyclization intermediate **B** or **C**. It should be noted that another possible pathway for the formation of intermediate **B** maybe through the stepwise spiroindolization/migration sequence via intermediate **D**.[11] Next, a hydroxyl substituted *N*H free carbazole product could be generated preferentially through the aromatization of intermediate **B**. Besides, we anticipated that the symmetric carbazole product could be formed when a nonsubstituted pyrrole is used instead of indole. If the hypothesis is successful, it will provide rapid access to various synthetically valuable symmetric and unsymmetric hydroxyl substituted *N*-H carbazoles from readily available starting materials in an efficient manner with high atom economy.

To study the feasibility of the hypothesis, we initially chose the 1,4-diphenylbut-3-ene-1,2-dione **1a** and the indole **2a** as reactants in the model reaction (Table 1). To our delight, the carbazole compound **3a** was obtained as the only product in 69% isolated yield when $Cu(OTf)_2$ was used as the catalyst in THF at 70 ºC for 2.5 hours (entry 1). Encouraged by this initial result, the effect of catalysts was subsequently investigated. First, the examination on other metal triflates (entries 2−5) indicated that $Cu(OTf)_2$ was clearly the better choice for this carbazole formation reaction. For instance, only trace of product **3a** was detected by TLC when $Sc(OTf)_3$ or $Y(OTf)_3$ was employed as the catalyst (entries 4 and 5). Next, two copper catalysts, $CuCl_2$ and $CuSO_4$, were examined under the similar reaction conditions and a low yield of **3a** was obtained, respectively (entries 6 and 7). Subsequently, the reaction was verified using $Cu(OTf)_2$ as the catalyst in the presence of several solvents (entries 8-12); 1,4-dioxane was found to be the best to obtain the corresponding carbazole **3a** in 79% yield at 70 °C for 2.5 hours (entry 8). Further adjustments showed a noticeable effect on the reaction temperature, which gave an 88% yield of the product at 80 °C (entries 13–15). Finally, the conditions in entry 14 (Table 1) were identified as the optimal conditions.

Table 2. Scope of substituted but-3-ene-1,2-dione derivatives.[a]



[a] Reaction conditions: **1a-p** (0.45 mmol), **2a** (0.3 mmol) and $Cu(OTf)_2$ (0.03 mmol) in 4.0 mL of dioxane at 80 °C and isolated yields were reported. [b] The reaction was performed on a gram scale.

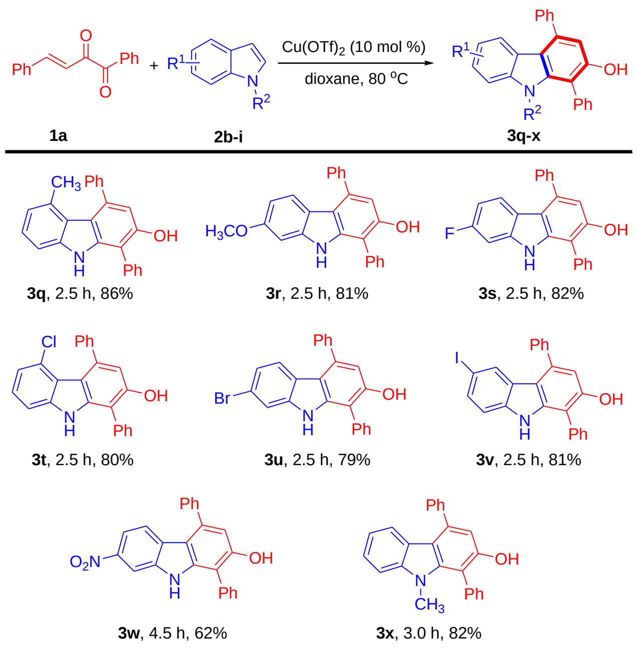
With the optimized reaction conditions in hand, we next focused our attention on substrate scope to determine the generality of this carbazole formation reaction. As illustrated in Table 2, we initially focused on the 1,4-disubstituted but-3-ene-1,2-diones, which were easily prepared according to the reported literature.[10a,12] Substrates bearing various substituents on the phenylring of R^1 proved reactive with little variation the yields of the isolated products **3a–j**. For example, 1,4-disubstituted but-3-ene-1,2-diones bearing alkyl, methoxyl or halide groups on the 3 or 4-position of the phenyl rings gave the corresponding products (**3b-i**) in good yields. In addition, substrate with an ortho-substituted aromatic ring of R^1 needed longer reaction time and gave slightly lower yield of the product **3j**, probably due to the steric hindrance effect. A selection of substrates displaying R^2 substituent of but-3-ene-1,2-diones was then examined. Under standard reaction conditions, various substituents on the aromatic ring of R^2 were all compatible with the present method and afforded the corresponding carbazole products in good yields (**3k-m**). However, the substrate containing a nitro group on the aromatic ring of R^2 did not yield any desired carbazole product (**3n**). Moreover, only a complex mixture was obtained with an alkyl substituted conjugated diketone **1o** or **1p** under the standard conditions (**3o** and **3p**). Importantly, an effective gram-scale synthesis of **3a** (2.11 g, 74%) was carried out to demonstrate the scalability of this transformation. Finally, the structure of **3i** was unambiguously confirmed by X-ray crystallographic analysis (Figure 2).[13]


3i **5c**

Figure 2. X-Ray structure of **3i** and **5c**.

Next, the reaction scope of the indoles was examined (Table 3). The results indicated that a broad spectrum of substituted indoles can be employed in this transformation and affording the desired carbazole products **3q-x** in moderate to good yields. Specifically, an iodo substituent on the 5-position is well tolerated, thus allowing post-reaction transformation of **3v** through a series of cross coupling chemistry. Moreover, a strong electron-withdrawing group, such as nitro, was also compatible with the present catalytic system and afforded the carbazole **3w** in 62% yield, albeit with a longer reaction time. More interestingly, *N*-methyl substituted indole **2i** also successfully underwent the

Table 3. Scope of substituted indole derivatives.[a]

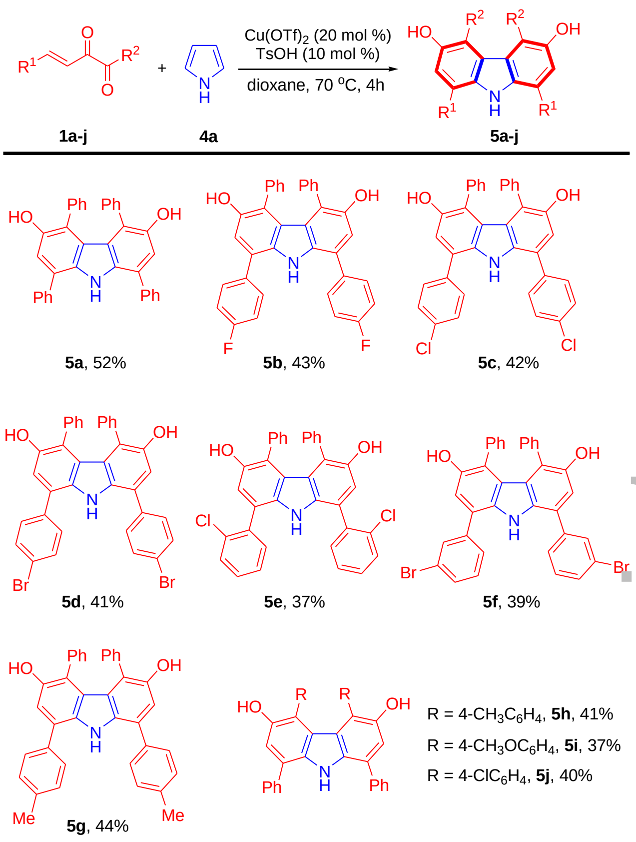


[a] Reaction conditions: **1a** (0.45 mmol), **2b-i** (0.3 mmol) and Cu(OTf)$_2$ (0.03 mmol) in 4.0 mL of dioxane at 80 °C and isolated yields were reported.

reaction to afford the carbazole product **3x** in high yield.

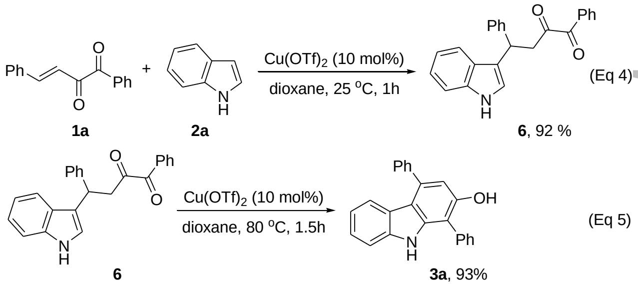
Naturally, as we envisioned in Scheme 1, we decided to test the more challenging pyrrole substrate in order to gauge the full capability of this interesting method.[14, 15] We found that under slightly modified reaction conditions, the synthetically valuable symmetric densely substituted and hydroxyl containing carbazoles were formed in moderate yields (Table 4). It should be noted that increasing the loading of the copper catalyst as well as the addition of TsOH (10 mol%) are necessary for the promotion of the reaction. Subsequent investigation indicated that a series of substituents on the phenyl ring of both R^1 and R^2 in the substituted but-3-ene-1,2-diones were all compatible with the present catalytic system and afforded the desired symmetric carbazoles in acceptable yields (**5a–j**). Moreover, the structure of the product **5c** was also confirmed by X-ray crystallographic analysis (Figure 2).[13]

Table 4. Synthesis of symmetric carbazoles from various substituted but-3-ene-1,2-diones with pyrrole.[a]



[a] Reaction conditions: **1** (0.9 mmol), **4a** (0.3 mmol), Cu(OTf)$_2$ (0.06 mmol) and TsOH (0.03 mmol) in 4.0 mL of dioxane at 70 °C for 4 hours and isolated yields were reported.

For the mechanistic studies of this transformation, two control experiments were carried out carefully (Scheme 3). First, we successfully isolated the C3-alkylated intermediate **6** of indole in 92% yield by decreasing the reaction temperature to 25 °C (Eq 4). Subsequently, the compound **6** afforded the desired carbazole product **3a** in 93% yield when it was heated under the standard conditions at 80 °C (Eq 5). These results and the X-ray structures of the products are strongly supported our initial hypothesis of the possible reaction pathway as shown in Scheme 1. The driving force for the selective annulation at C1 position of intermediate **6** could be attributed to the formation of six member ring and aromatization process.



Scheme 3. Control experiments.

In conclusion, we have developed a new methodology, thus allowing the selective annulation of a but-3-ene-1,2-dione with an unprotected indole or pyrrole derivative leading to both symmetric and unsymmetric hydroxyl containing *N*-H carbazoles with the use of $Cu(OTf)_2$ as an efficient catalyst. Simple and readily available starting materials, broad substrate scope, inexpensive copper catalyst and high atom economy make this transformation more efficient. Moreover, the presence of a free hydroxyl as well as an amino group on the carbazole products makes it possible for chemists to transformation further according to demand. We foresee that this general and operationally simple approach can provide direct access to various symmetric and unsymmetric carbazole compounds and might have a major impact on the synthesis of structurally complex molecules, functionalized materials, and pharmaceuticals.

Experimental Section

General procedure for the $Cu(OTf)_2$-catalyzed reaction of but-3-ene-1,2-diones with indoles

To a solution of but-3-ene-1,2-dione (0.45 mmol) and indole (0.3 mmol) in dioxane (4.0 mL) was added $Cu(OTf)_2$ (0.03 mmol) under an air atmosphere. The resulting mixture was heated at 70 °C for the indicated time. After completion of the reaction, the mixture was cooled to room temperature. The solvent was removed in a vacuum, and the resulting residue was purified on a silica gel column (petroleum ether/EtOAc = 10:1) to provide the desired products **3**.

General procedure for the preparation of symmetric carbazoles from pyrrole

To a solution of but-3-ene-1,2-dione (0.9 mmol) and pyrrole (0.3 mmol) in dioxane (4.0 mL) was added $Cu(OTf)_2$ (0.06 mmol) under an air atmosphere. The resulting mixture was stirred at room temperature for 1 h, and then TsOH (0.03 mmol) was added. Next, the mixture was heated at 70 °C for 4 hours. After completion of the reaction, the mixture was cooled to room temperature. The solvent was removed in a vacuum, and the resulting residue was purified on a silica gel column (petroleum ether/EtOAc = 10:1) to provide the desired products **5**.

Acknowledgements

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COMMUNICATION

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