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COMMUNICATION

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Brønsted Acid-Catalyzed Synthesis of Carbazoles from 2-Substituted Indoles

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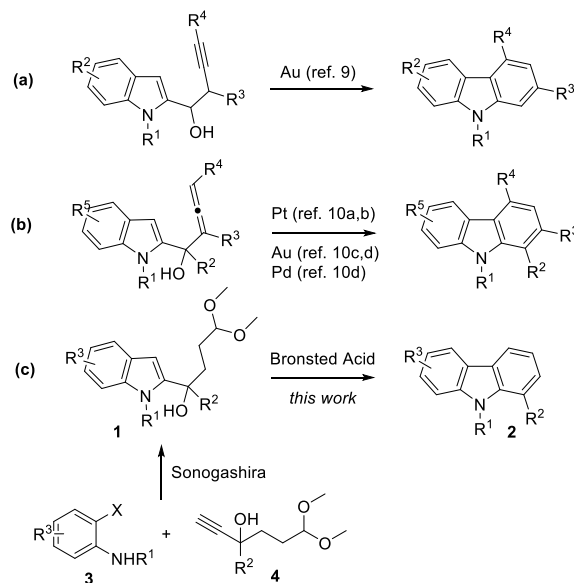
A simple and efficient method for the synthesis of disubstituted carbazoles has been developed. In this approach, carbazoles are synthesized from *o*-haloanilines and terminal alkynes using a two-step strategy, namely, Sonogashira coupling and an intramolecular cyclization to provide indoles, which are followed by a *p*-TSA·H₂O-catalyzed carbazole formation.

Tricyclic carbazole nucleus is one of the most important heterocycles since it is not only found in many natural products and bioactive molecules¹ but also broadly served as building blocks for potential electroluminescent materials² due to its special thermal³ and electrical⁴ properties, as well as host materials for triplet emitters in organic light-emitting diodes.⁵ Accordingly, a variety of well-documented traditional and modern methods have been developed for the construction of carbazoles and their derivatives.^{6,7} These synthetic methods are mainly classified into two broad categories: one is the formation of the pyrrole core from biphenyls, and the other is the formation of a benzene ring from indoles. However, these literature methods have suffered from some drawbacks such as harsh reaction conditions, low yields, and poor atom economy. Therefore it is still of interest to uncover new synthetic methods for the realisation of these important molecules.

Synthetic pathways towards carbazoles from indoles have drawn a great deal of attention because indole substances abundantly exist.⁸ For example, Ma and coworkers reported a Au-catalyzed cyclization of 1-(indol-2-yl)-3-alkyn-1-ols for the synthesis of carbazoles (Scheme 1a).⁹ Cyclization reaction of 1-(indol-2-yl)-2,3-allenols involving Pt,^{10a-10b} Au,^{10c-10d} and Pd^{10d}-catalysis were also achieved by Ma and Alcaide, respectively (Scheme 1b). Knölker also reported the many application of iron-mediated^{10e-10j} and palladium-catalysed^{10k-10q} approaches for the synthesis of carbazole derivatives. In 1995, Mahboobi reported a carbazoles synthesis from 1-(*N*-Benzylindol-2-yl)-3-(1,3-dioxolan-2-yl)propan-1-ol in the presence of HCl, but only one example was recorded.¹¹ In this paper, we

report herein our preliminary results on the synthesis of disubstituted carbazoles using a two-step procedure from *o*-haloanilines **3** and terminal alkynes **4** (Scheme 1c).

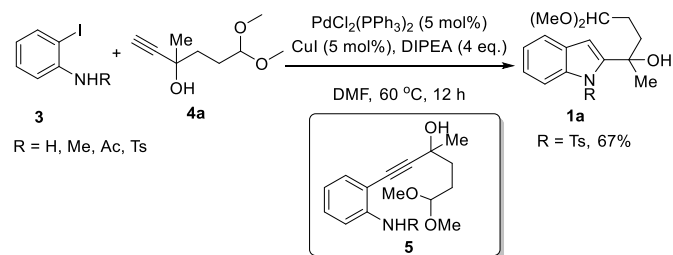
Scheme 1. Carbazoles synthesis from indoles.



In order to introduce different substitutes on the indole ring, the starting materials, **1a-j**, are prepared mainly through a Sonogashira¹² coupling reaction and then with an intramolecular cyclization, starting from *o*-haloanilines **3** and terminal alkynes **4**. We initiated our studies by examining different protecting groups of **3** with terminal alkyne **4a** under classical Sonogashira conditions. When R was H, Me, or Ac, indole products were not given, but only the direct Sonogashira coupling product **5** was generated. However, a Ts

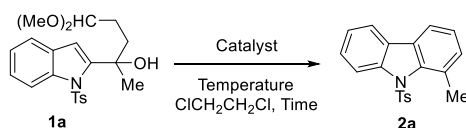
protecting group was found to give the desired indole product **1a** with an acceptable yield of 67% (Equation 1).

Equation 1. Protecting group's effect on **3** to form indole **1**.



After determining the optimal protecting group, we turned our attention to the optimization of the carbazole formation reaction conditions. 5,5-Dimethoxy-2-(1-tosyl-1*H*-indol-2-yl)pentan-2-ol **1a** was employed as a model substrate. A variety of reaction conditions (catalyst, temperature) were examined and some of the representative results are shown in Table 1. It was found that *p*-TSA•H₂O was more effective than the other acids, such as Amberlyst 15, albeit capable of promoting the reaction but with lower yield (entries 1, 2). When the reaction was conducted at a higher temperature (40 °C), it rapidly gave the carbazole product in 95% yield within 1.5 h (entry 3). Decreasing the amount of catalyst to 20 mol% and prolonging the reaction time to 3 h led to the best result (entry 4).

Table 1. Reaction optimization.^a



Entry	Catalyst (eq.)	Temperature (°C)	Time (h)	Yield (%) ^b
1	Amberlyst 15 (2)	40	14	69
2	<i>p</i> -TSA•H ₂ O (2)	23	48	93
3	<i>p</i> -TSA•H ₂ O (2)	40	1.5	95
4	<i>p</i> -TSA•H ₂ O (0.2)	40	3	96

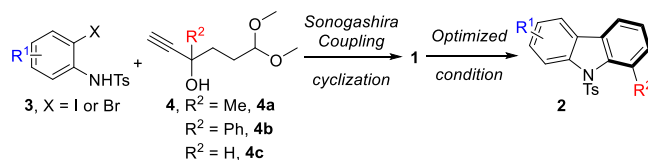
^a Reaction conditions: **1a** (0.2 mmol), catalyst, in ClCH₂CH₂Cl (2 mL). ^b Isolated yield.

With the optimized conditions in hand, we next investigated the substrate scope of this reaction. As illustrated in Scheme 2, the transformation was found to be very general. Various substituted indoles can successfully give the corresponding carbazole derivatives (**2a-2h**). However, electron-withdrawing groups (F, NO₂, and CF₃) on indole slowed down the reaction, and needed higher temperature (60 °C), but products were still isolated in moderate to good yields (56%-85%) (**2f-2h**). Moreover, R² could also be an aryl group (**2i**), or H (**2j**).

A plausible mechanism for the annulation of 5,5-dimethoxy-2-(1-tosyl-1*H*-indol-2-yl)pentan-2-ol **1a** catalyzed by *p*-TSA•H₂O is presented in Scheme 3. The intermediate acetal **6** is formed through the elimination of MeOH from indole **1a** in the presence of *p*-TSA•H₂O, which was also isolated as diastereoisomers in a nearly

1:1 ratio. Then successive elimination of water/MeOH from intermediates **7** and/or **8** could give carbazole product **2a**.¹³

Scheme 2. Sonogashira coupling for indole synthesis and *p*-TSA•H₂O-catalyzed carbazole synthesis.^a

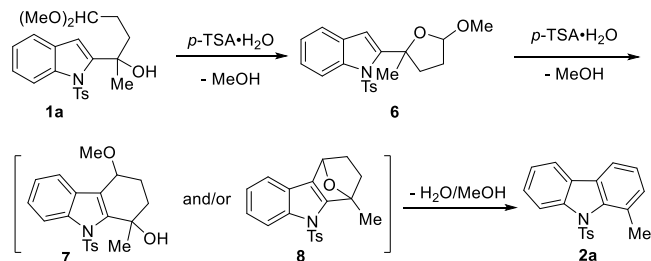


entry	3	4	1	2
1		4a	1a , 67%	
2		4a	1b , 75%	
3		4a	1c , 66%	
4		4a	1d , 49%	
5		4a	1e , 64%	
6		4a	1f , 92%	
7		4a	1g , 48%	
8		4a	1h , 69%	
9		4b	1i , 77%	
10		4c	1j , 62%	

^a Indole synthesis conditions: **3** (0.8 mmol), **4** (0.88 mmol), PdCl₂(PPh₃)₂ (0.04 mmol), CuI (0.04 mmol), *N,N*-diisopropylethylamine (3.2 mmol), DMF (2 mL), at 60 °C for 12 h,

isolated yield. Carbazole synthesis conditions: **1** (0.2 mmol), *p*-TSA•H₂O (0.04 mmol), ClCH₂CH₂Cl (2 mL), at 40 °C for 3 h, isolated yield. ^b At 60 °C.

Scheme 3. A Plausible Mechanism.



Conclusions

In summary, we have developed a simple and efficient two-step approach (Sonogashira/intramolecular cyclization for indole synthesis and *p*-TSA•H₂O-catalyzed carbazole synthesis) for the synthesis of diversified substituted carbazoles from *o*-haloanilines **3** and terminal alkynes **4** in good isolated yields under mild conditions. Because of the ready availability of the starting materials and the potential of the products, this method should be useful in organic synthesis and medicinal chemistry. Further studies on the synthetic applications of this reaction are in progress in our laboratory.

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Notes and references

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