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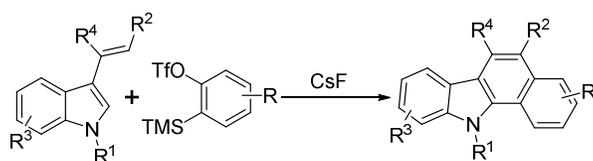


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COMMUNICATION

Construction of Benzo[a]carbazole Derivatives via Diels-Alder Reaction of Arynes with Vinylindoles

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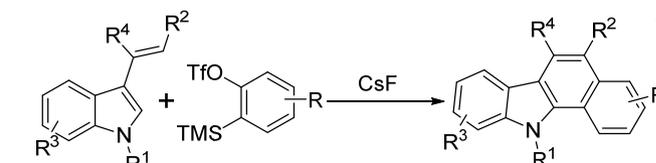
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A new protocol for high-efficiency and versatile Diels-Alder reaction of vinylindoles with arynes (generated from 2-(trimethylsilyl)aryl triflate) has been developed. A various functionalized benzo[a]carbazoles were afforded in good to perfect yields via [4 + 2] cycloaddition/aromatization.

Carbazoles are an important class of heterocycles and have gained extensive interest of scientists not only because of the observably biological activity¹ but also due to their unique optical properties.² Benzo[a]carbazoles, as a subunit of carbazoles, have also received much attention, which exhibit a broad range of pharmacological activity,³⁻⁶ such as antitumor,³ anti-inflammatory⁴ and antiestrogenic properties,⁵ or kinase inhibitory activities.⁶ Therefore, great efforts were directed toward the development of efficient synthetic methods for the preparation of this privileged framework with various substitution patterns in the past decades,⁷⁻¹⁰ and most of representative approaches have focused on: (a) the Fischer-Borsche reaction of various substituted quinolyhydrazones or iso-quinolyhydrazones,⁷ (b) transition-metal-catalyzed cyclization reactions of indole derivatives;⁸ (c) cascade cyclization of diynes;⁹ (d) intramolecular photoinduced cyclization of indole derivatives.¹⁰ Although these procedures are useful and general, there are still some restrictions such as the preparation of raw materials, poor atom economy and the cost of the catalytic system. Thus, it is highly desirable to provide the efficient and facile strategies for the preparation of benzo[a]carbazole derivatives.

In the last century, Pindur and co-workers have reported a new route to the synthesis of benzo[a]carbazoles via the arynes (generated from *o*-benzenediazonium carboxylate) Diels-Alder reaction with 3-vinyl-indoles,¹¹ but the reaction was limited due to the harsh conditions with low yields. In recent years, 2-(trimethylsilyl)aryl triflates, as the aryne precursors, have been

broadly used for the preparation of cyclic compounds via addition under mild reaction conditions.¹² As part of our ongoing studies on the development of arynes chemistry,¹³ we continued to explore the feasibility of synthesizing useful and biologically important compounds by Diels-Alder reaction of dienes with 2-(trimethylsilyl)aryl triflates.¹⁴ After a series of trial, we have successfully developed an efficient, mild reaction of vinylindoles with 2-(trimethylsilyl)aryl triflates by the Diels-Alder reaction leading to the synthesis of benzo[a]carbazole derivatives in good to perfect yields. Herein, we wish to detail our results.



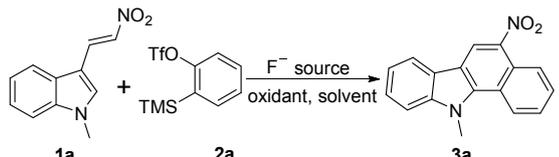
Scheme 1 Reaction of Vinylindoles and Arynes

Initially, the reaction of 1-methyl-3-(2-nitrovinyl)-1H-indole (**1a**) with 2-(trimethylsilyl)aryl triflate (**2a**) was chosen as a model reaction to screen the optimal reaction conditions, and the results are summarized in table 1. To our delight, treatment of **1a** with **2a** using 3.0 equiv of CsF in 2 mL CH₃CN at 80 °C under an open air atmosphere afforded the corresponding benzo[a]carbazole (**3a**) in a 83% yield (entry 1). Encouraged by this result, a series of other solvents, including THF, toluene and dioxane were tested, and the results showed that they are unfavourable to the cycloaddition reaction (entries 2-4). Then, KF and TBAF were investigated as fluoride sources, and it was found that they both were less effective than CsF (entries 5- 6). The product yield of **3a** was increased to 91% when the reaction was carried out under O₂ atmosphere (entry 7). However, the replacement of O₂ with N₂ led to a low yield (entry 8). Obviously, these experiments revealed that oxidants are necessary for the oxidative aromatization of the cycloaddition product. Therefore, different oxidants such as TBHP, DDQ, PhI(OAc)₂ and m-CPBA were examined (entries 9-12), and the results indicated that the oxidant O₂ is the best choice for this transformation. Further examination of the reaction temperature showed that **3a** could be obtained in 95% isolated yield at 60 °C (entries 13 and 14). Thus, the optimized reaction conditions were as follows: **1a** (0.3 mmol), **2a** (0.45 mmol), CsF (0.9 mmol), in CH₃CN (2 mL) at 60 °C under O₂ atmosphere.

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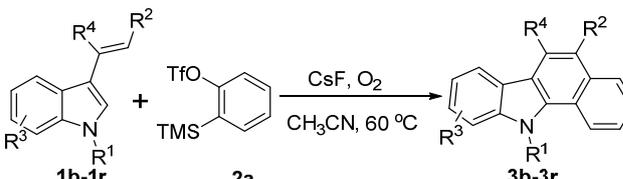
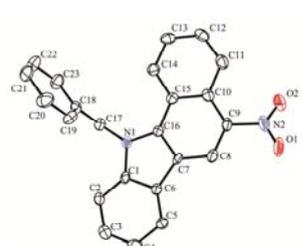
Table 1 Optimization of Reaction Conditions^a


Entry	Solvent	F ⁻ Source	Oxidant	Yield (%) ^b
1	CH ₃ CN	CsF		83
2	THF	CsF		trace
3	Toluene	CsF		nr
4	Dioxane	CsF		nr
5	CH ₃ CN	KF		56
6	CH ₃ CN	TBAF		trace
7 ^c	CH ₃ CN	CsF		91
8 ^d	CH ₃ CN	CsF		21
9	CH ₃ CN	CsF	TBHP	52
10	CH ₃ CN	CsF	DDQ	trace
11	CH ₃ CN	CsF	PhI(OA) ₂	46
12	CH ₃ CN	CsF	m-CPBA	45
13 ^{c,e}	CH ₃ CN	CsF		95
14 ^{c,f}	CH ₃ CN	CsF		88

^a Unless otherwise noted, reactions were carried out on a 0.3 mmol scale of **1a** with 1.5 equiv of **2a**, F⁻ source (3.0 equiv), and oxidant (1.0 equiv) in solvent (2.0 mL) at 80 °C under air atmosphere, 6 h. ^b Isolated yields; nr: no reaction. ^c Under O₂. ^d Under N₂. ^e At 60 °C. ^f At 50 °C.

With the optimized conditions in hand, the scope of this cycloaddition reaction of various substituted vinylindoles **1a** with 2-(trimethylsilyl)phenyl triflate **2a** was investigated, and the results are summarized in table 2. Initially, 3-(2-nitrovinyl)indoles with a different substituents on the nitrogen atom were screened. The results demonstrate that various N-substituted vinylindoles could be smoothly transformed into the desired products (**3b-3f**). For examples, N-cyclopropylmethyl and N-benzyl substituted 3-vinylindoles, were well tolerated in the cycloaddition reaction providing **3b** and **3c** in 87% and 85% yield respectively, and the structure of **3c** was unambiguously confirmed by single crystal X-ray analysis (Figure 1). Importantly, the substrates **1d** and **1e** bearing N-allyl or N-propargyl groups respectively, were translated into the expected products **3d** and **3e** in good yields. We next also evaluated the R² group (R² = EWG), such as CPh, COMe, COOMe and CN, and the results indicated that the corresponding desired products (**3g-3j**) were obtained in 94-99% yield under the optimized reaction conditions. Unfortunately, when the R² group was methyl or phenyl, the desired products couldnot be isolated. These results indicated that the Diels-Alder reaction with inverse-electron-demand is dominated by the interaction of the HOMO of the electron-rich aryne and the LUMO of the electron-deficient vinylindole.¹⁵ Subsequently, the group R³ on the benzene ring of the indole moiety were tested, whether electron-donating groups such as Me and OMe or electron-withdrawing groups such as F, Cl and Br were reacted smoothly and provided corresponding cycloaddition products (**3k-3p**) in perfect yields (96%-99%). These results indicated that the electronic or steric effect on the benzene ring did not play a significant role in regulating the reaction. Finally, tri-substitued vinyl indoles were investigated.

When the R⁴ group was methyl or phenyl, the corresponding products **3q** and **3r** were obtained in good yields.

Table 2 Cycloaddition Reaction of vinylindoles (**1**) with Aryne Precursor (**2a**)^{a,b}



3b , 87%	3c , 85%	3d , 83%
3e , 75%	3f , 72%	3g , 96%
3h , 99%	3i , 94%	3j , 99%
3k , 97%	3l , 96%	3m , 98%
3n , 98%	3o , 99%	3p , 97%
3q , 85%	3r , 88%	

^a Reaction conditions: **1** (0.3 mmol), **2a** (0.45 mmol), and CsF (0.9 mmol), in CH₃CN (2 mL) at 60 °C under O₂ atmosphere, 6 h. ^b Isolated yields.

Figure 1. OPTEP structure of **3c**.

To expand the scope of this [4 + 2] cycloaddition methodology, various substituted aryne precursors (**2b-2e**) were examined (Table 3). Under the optimized reaction conditions, the *o*-silyl aryltriflates bearing methyl, F, or Cl group on the aryl moiety, could effectively react with **1g**, and afforded the target products in perfect yields. These results shown the reactivity was not affected by the electronic effect of the arynes. However, these unsymmetrical arynes generated from substrates **2c** and **2e**, which provided two regioisomers, respectively, in a 1.1 : 1 ratio and a 1 : 1 ratio. The lack of regioselectivity of the reaction is consistent with the intermediate of arynes, and clearly supported that the reaction takes place through a [4 + 2] cycloaddition.

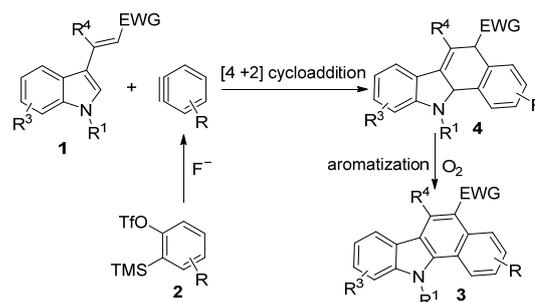
Table 3 Cycloaddition Reaction of Vinylindole (**1g**) with Aryne Precursors (**2**)^{a,b}

Entry	Substrate 2	Product 3 ^b (%)
1		
2		
3		
4		

^a Reaction conditions: **1** (0.3 mmol), **2** (0.45 mmol), and CsF (0.9 mmol), in CH₃CN (2 mL) at 60 °C under O₂ atmosphere, 6 h. ^b Isolated yields.

On the basis of our research and the previously reported mechanism,¹²⁻¹⁴ a reasonable mechanism is illustrated in scheme 2. Firstly, aryne could be generated in situ from 2-(trimethylsilyl)phenyl triflate **2** by the fluoride-induced 1,2-elimination. Subsequently, the 3-vinyl-indole **1** as diene reacts

with aryne, and affords the intermediate **4** via the [4 + 2] cycloaddition reaction. Finally, intermediate **4** undergoes aromatization to gain the desired benzo[*a*]carbazoles **3** under O₂ atmosphere.



Scheme 2 Possible Mechanism

In conclusion, we have developed a new protocol for high-efficiency and mild Diels-Alder reaction of 3-vinyl-indoles with arynes. The reaction allows the synthesis of various benzo[*a*]carbazole derivatives with excellent yields, which are significant structural units in a number of biologically active compounds. In addition, the cycloaddition reaction could be performed under transition-metal-free conditions and therefore represents an efficient and environmentally benign protocol for the synthesis of benzo[*a*]carbazoles.

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