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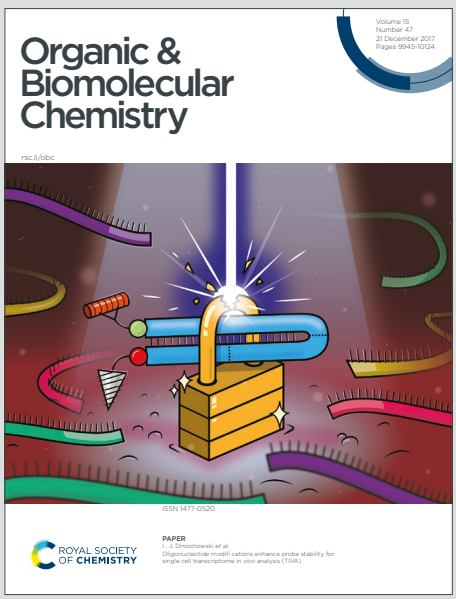

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PAPER

One-pot access to tetrahydro benzo[*c*]carbazole from simple ketones by using O_2 as oxidant

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An effective and operationally simple one-pot Brønsted acid catalyzed cascade method is demonstrated for the synthesis of diversely functionalized carbazole frameworks starting from protecting group free 2-alkenyl indoles. The employment of easily available unactivated ketones as annulating partners, mostly unexplored for the synthesis of carbazoles, is the major highlight of this protocol. This protocol is step- and atom-economic, molecular oxygen was used as the green oxidant, water was the only by-product and amenable to different functional groups. Moreover, gram-scale synthesis and downstream modification of the obtained products demonstrate the synthetic applicability of this protocol.

Carbazoles and benzocarbazoles are privileged class of aza-heterocycles embedded in many naturally occurring alkaloids and synthetic compounds that exhibit a wide range of attractive biological activities (Figure 1).[1-2]

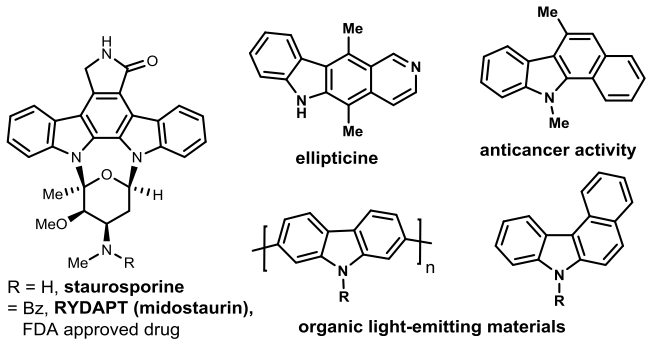

Fig. 1. A few significant carbazole derivatives.

In addition, these aza-heterocycles serve as key building blocks for the design of OLED materials, electroluminescent and hole transport materials, and photoconductors due to their wide band gap and promising optoelectronic properties.[3]

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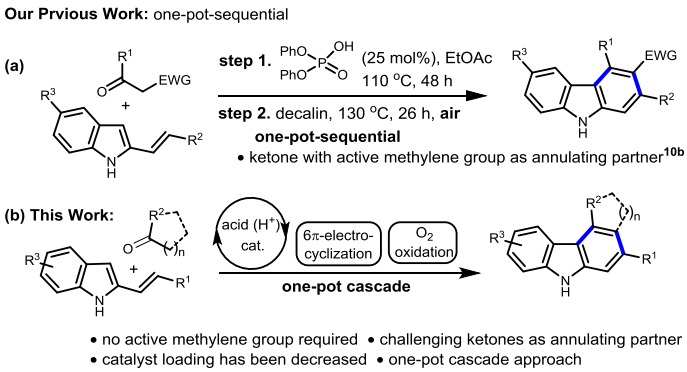
Owing to the ever-increasing potential applications of aza-heterocycles, the facile and efficient methods are still required for acquiring polyfunctionalized carbazoles which will be the immediate precursors of benzo[*c*]carbazoles[4-5] in one-pot pathway.[6] A plethora of synthetic approaches for the construction of carbazoles can be categorized into two primary modes, first, construction of the internal pyrrole ring from arene frameworks through C–C[7] or C–N[8] bond formation. A second strategy, namely benzannulation,[9] has gained increasing importance in the recent years due to ready access to the diverse indole derivatives. However, these protocols often entail multistep endeavours, harsh reaction conditions, restricted to specific starting materials, use of precious metal catalysts and required either stoichiometric amount of expensive oxidant or dehydrogenating agent like DDQ or Pd/C, thus revealing their limitations.

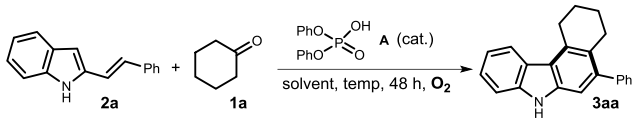


Scheme 1 Previous Reports and this Strategy.

Therefore, devising elegant approach is highly desirable to access diversely functionalized carbazoles by employing readily available starting materials as well as catalysts in order to curtail the aforementioned limitations. Inspired by the synthetic challenges, and as a part of our continuing research program on Brønsted acid catalysis,[10] we anticipated that carbazole can be prepared by one-pot Brønsted acid catalyzed benzannulation pathway using simple and ubiquitous ketones, specifically cyclic

ketones. But comparatively lesser reactivity of ketones due to the lack of electrophilic nature and steric influence make the nucleophilic attack more challenging. In 2018,[10b] our group have reported a benzannulation strategy using active methylene group to get versatile substituted carbazoles, however under the similar reaction conditions ketones failed to provide carbazoles (Scheme 1). These challenges prompted us to develop a fresh route to handle the problem and, herein, we reveal our result on Brønsted acid catalyzed one-pot cascade benzannulation strategy using simple ketones as annulating partner to access wide varieties of NH-free carbazoles. To our delight, advancement of this method has been achieved via curtailing multistep sequential method to one pot cascade annulation strategy using oxygen[11] as sole oxidant.[12] This method showed an excellent route for the rapid generation of benzo[*c*]carbazoles precursors from 2-alkenyl indoles in one pot. Worthy to mention, this method does not require first generation of 3-alkenyl indole via sulfone formation strategy.[10a]

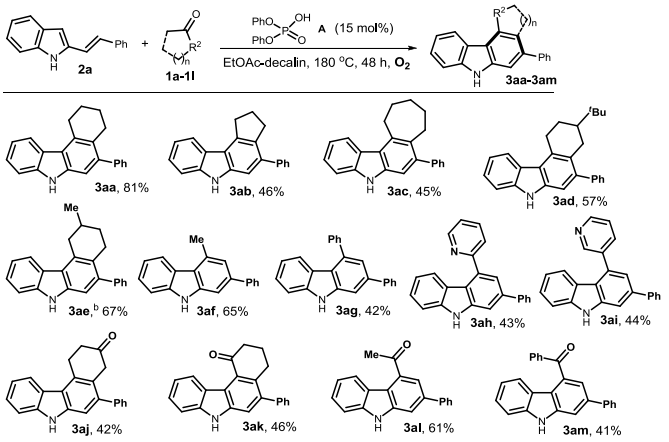
Table 1. Optimization of the Reaction Conditions[a]



entry	acid cat. (mol%)	solvent	Temp (°C)	yield (**3aa**%)[b]
1	25	EtOAc-decalin	180	75
2	25	EtOAc-decalin	130	53
3	25	EtOAc-xylene	180	51
4	25	EtOAc-DMSO	180	ND
5	25	decalin	180	<10
6	**15**	**EtOAc-decalin**	**180**	**81**
7	10	EtOAc-decalin	180	61
8[c]	15	EtOAc-decalin	180	43
9[d]	15	EtOAc-decalin	180	55
10[e]	15	EtOAc-decalin	180	<10
11[f]	15	EtOAc-decalin	180	75
12	15	EtOAc-decalin	130	37

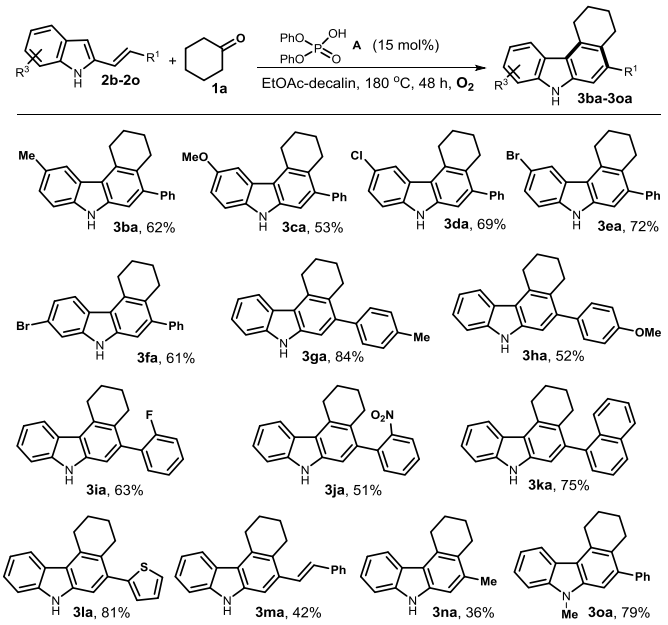
[a]Reaction conditions: **1a** (0.30 mmol), **2a** (0.15 mmol). [b]Isolated yield. [c]PTSA·H_2O was used as catalyst. [d]Air as oxidant. [e]N_2 in place of O_2. [f](*Z*)-**2a** was used in place of (*E*)-**2a**.

Keeping this strategy in mind, the optimization of the reaction conditions was initiated by choosing (*E*)-2-styryl-1*H*-indole **2a** and commercially available cyclohexanone **1a** as model substrates under molecular oxygen as sole oxidant. By conducting the reaction using readily available diphenyl phosphate as catalyst (25 mol%) in EtOAc-decalin mixed solvent at 180 °C furnish carbazole **3aa** in 75% yield (Table 1, entry 1). On decreasing the reaction temperature, the yield decreased to 53% (entry 2) and other mixed solvents did not give better outcome (entries 3-5). Upon varying the catalyst loading, highest yield of **3aa** was recorded when 15 mol% catalyst was employed (81%, entries 6-7). Yield of the reaction decreased to 43% upon employing a stronger Brønsted acid catalyst (entry 8). It has been found that concentration of oxygen plays a crucial role for the oxidative aromatization reaction as on executing the reaction using air as a source of the molecular oxygen, yield of the reactions diminished significantly (entry 9). On conducting the reaction under N_2 instead of oxygen, yield of the reaction decreased drastically (entry 10). The (*E*)-**2a** was more effective as the corresponding (*Z*)-isomer provided **3aa** in 75% yield (entry 11). On decreasing the reaction temperature, the yield of the reaction decreases drastically due to incomplete consumption of different intermediates (entry 12).



[a]Reaction conditions: **2a** (0.20 mmol), **1a**-**1l** (0.40 mmol), **A** (15 mol%), EtOAc-decalin, 180 °C; isolated yield. [b]**3ae** was isolated along with its second regioisomer.

Scheme 2 Scope of Electrophiles[a].



[a]Reaction conditions: **2b**-**2o** (0.20 mmol), **1a** (0.40 mmol), **A** (15 mol %), EtOAc-decalin, 180 °C; isolated yield.

Scheme 3 Scope of 2-alkenylindoles[a].

To study the generality of this tandem benzannulation, at first several cyclic or acyclic ketones bearing no active methylene group were reacted with **2a**. Cyclopentanone and cycloheptanone provided carbazoles **3ab** and **3ac** in modest yields (Scheme 2). 4-*tert*-Butylcyclohexanone also reacted smoothly to furnish carbazole **3ad** in 57% yield. When unsymmetrical cyclohexanone was utilized, a mixture of

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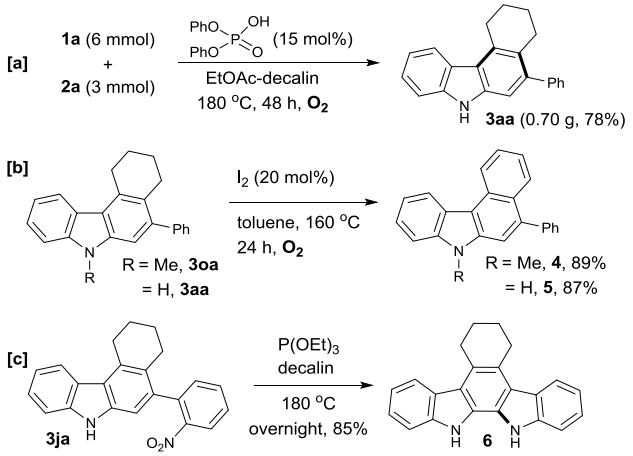
regioisomers **3ae** and **3ae'** were isolated in 67% overall yield (in 4.4:1 ratio). To our delight, acetone was found to be an elegant annulating partner furnishing carbazole **3af** in 65% yield. Pleasingly, even less reactive aryl ketones, namely acetophenone and acetylpyridines delivered carbazoles **3ag**-**3ai** in moderate yields. 1,4- and 1,2-Cyclohexanediones also reacted well to afford carbazoles **3aj** and **3ak** bearing a ketone functional group and hence providing opportunity for further downstream modifications. Butanedione and acetyl benzoyl are also suitable annulating partners to provide carbazoles **3al** and **3am** bearing a ketone moiety at the 4-position. The sterically hindered cyclopropyl methyl ketone and pinacolone failed to provide desired carbazoles.

Subsequently, a variety of substituted 2-alkenylindoles **2b**-**2o** were screened using cyclohexanone as an annulating partner. The 2-alkenylindoles bearing methyl, methoxy and chloride functional group at the 5-position afforded carbazoles **3ba**-**3da** in 53-69% yields. The 5- and 6-bromo substituted 2-alkenylindoles also reacted efficiently to provide the desired carbazoles **3ea** and **3fa** in 61-72% yields. Similarly, on varying alkene β–substitution with differently substituted aryl or heteroaryl groups, outcome of the reaction did not change (**3ga**-**3la**, 51-84% yields). Interestingly, albeit lower yield, styryl and alkyl groups at the 2-position of the carbazole can be installed successfully (**3ma**-**3na**, 36-42% yields). Although this annulation strategy is designed for protecting-group-free synthesis of diversified carbazoles, however *N*-methyl protected carbazole **3oa** can also be produced in 79% yield.



Scheme 4 Gram-Scale Synthesis and Synthetic Application.

To check the scalability of this annulation reaction, a gram-scale synthesis was carried out starting with 3 mmol of **2a** under standard reaction conditions and 0.7 g of product **3aa** was isolated (78% yield, Scheme 4a). Moreover, the desired benzo[*c*]carbazoles **4** and **5**, which show promising optoelectronic properties,[13] were successfully synthesized in 89% and 87% yields by following an iodine catalyzed aromatization reaction (Scheme 4b). Attempts to synthesize benzo[*c*]carbazole **4** and **5** in one-pot by adding catalytic amount of iodine after the formation of carbazoles were not successful. Next, Cadogan[14] reductive nitro group insertion onto the adjacent phenyl ring afforded symmetrical indolo[2,3-*a*]carbazole **6** in 85% yield.[15]

In conclusion, we have demonstrated an efficient, Brønsted acid catalyzed one-pot benzannulation strategy to access a rich assortment of diversified carbazoles from a variety of 2-alkenylindoles and appropriate ketones. Molecular oxygen as the green oxidant and water as sole by-product render this method economically as well as environmentally benign. In addition, efficacy of this new protocol has been reinforced through gram scale synthesis and easy aromatization to furnish benzocarbazole compounds.

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