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Indole-to-Carbazole Strategy for the Synthesis of Substituted Carbazoles under Metal-Free Conditions

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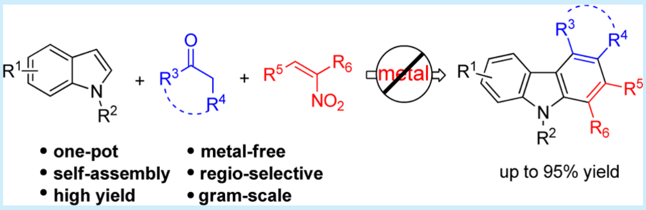
Ⓢ *Supporting Information*

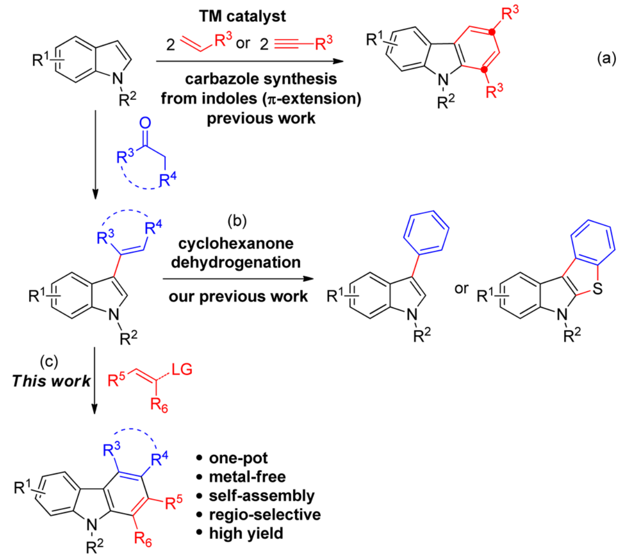
ABSTRACT: An efficient indole-to-carbazole strategy has been developed under metal-free conditions. This carbazole formation was highly promoted by NH_4I with high regioselectivity through formal [2 + 2 + 2] annulation of indoles, ketones, and nitroolefins. It thus conveniently enabled the assembly of a large number of diversified carbazole products with good tolerance of a broad range of functional groups.



Carbazoles represent an important class of nitrogen-containing heterocyclic compounds, many of which have found a wide range of applications as biologically active agents in medicinal chemistry.[1] Additionally, the carbazole moiety has found applications as a key building block in materials science, especially as organic light-emitting materials, due to its wide band gap and high luminescent efficiency.[2] Given the tremendous importance of carbazoles to those fields, various synthetic methods have been developed to construct functionalized carbazoles during the past several decades. While at an early stage the carbazole synthesis mainly relies on the Fischer−Borsche synthesis via a multistep procedure;[3] in recent years, intramolecular cross coupling by transition-metal (TM) catalysis for carbazole synthesis has been a subject of great interest.[4] Despite the primary efficiency of these methods, prefunctionalization of the precursors is an essential prerequisite in most cases.

Indole-based synthesis is still a hot field of research due to its significance in pharmaceutical chemistry and natural chemistry as well as synthetic methodology.[5] In this context, indole-to-carbazole transformation represents an advanced method for carbazole constructions, offering convenient opportunities to achieve desirable synthetic convergence and function-installing flexibility.[6] For example, the Miura group developed a Pd-catalyzed [2 + 2 + 2]cycloaddition of indoles with diarylacetylenes to give tetraarylated carbazoles. When terminal alkenes or alkynes were used, palladium, gold, and rhodium were successfully used as the catalysts to selectively provide 1,3-disubstituted carbazoles (Scheme 1a). In addition, the Itami and Lei groups cooperatively found that a Pd−Cu−Ag trimetallic system could convert indoles to carbazoles using electron-deficient alkenes. In our recent work, a formal cross-coupling of indoles with cyclohexanone as the aryl source has been well developed (Scheme 1b), in which 3-vinylindole was demonstrated as the key intermediate and it could readily transfer into 3-arylindoles[7a] and benzothieno[2,3-*b*]indoles[7b] under oxidative systems. On the basis of this observation and as our continuing interest in indole functionalization,[7c−e] we herein suppose a new carbazole assembly through oxidative annulations of the 3-vinylindole in situ formed and the third component as a two-carbon source such as alkenes, alkynes, etc. (Scheme 1c). In such a transformation, high regioselectivity could be expected, which thereby conveniently enables diversified carbazole products with a broad range of functional groups.

Scheme 1. Indole-to-Carbazole Transformations



Initially, we screened a range of alkenes under the previously mentioned DEPphos/O_2-based system (Scheme 2). While most of them were found to be unfruitful for the carbazole formation, styrene could serve as the two-carbon source for the

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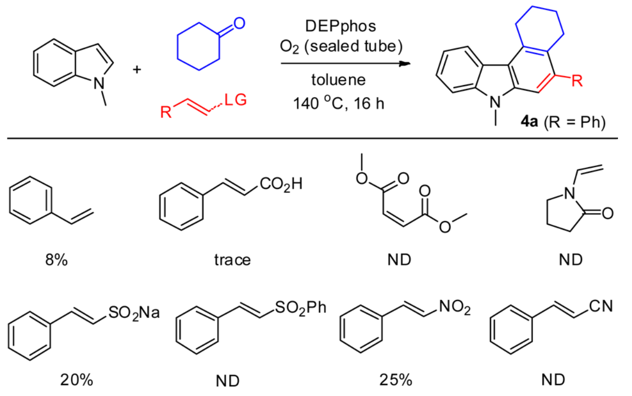
Scheme 2. Screening Different Alkenes for the Carbazole Formation

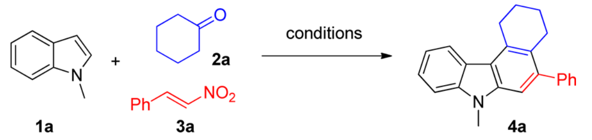


formal [2 + 2 + 2] cycloaddition, giving the carbazole **4a** in a low yield. To our delight, both the alkenyl sodium sulfonate and nitroolefin gave promising transformation of the desired reaction, generating the carbazole in 20% and 25% yield, respectively.

With these observations in hand, we next chose *N*-methylindole (**1a**), cyclohexanone (**2a**), and (*E*)-(2-nitrovinyl)-benzene (**3a**) as the model system to optimize the reaction conditions (Table 1). When various phosphorus reagents were used under air atmosphere, the intermediate 3-vinylindole could not be fully consumed in all cases (entries 1–3). These results triggered us to probe other kinds of catalysts. While N-heterocycles such as DMAP and 1,10-Phen afforded no desired products (entries 4 and 5), inorganic NH_4I enhanced the transformation to give the carbazole in good yield (entry 6). This catalyst might serve as a Brønsted acid to promote the reaction because elemental I_2, KI, and $(Me)_4NI$ could not improve the formation of **4a** (entries 7–9). However, the Brønsted acids such as AcOH, CF_3COOH, and TfOH could not give better results than NH_4I. We then screened the reaction atmosphere and reaction temperature (entries 10–13) and found the reaction performed under Ar at 150 °C gave a higher yield of the product (entry 12). Finally, excessive cyclohexanone (**2a**) was found to be the key for a full consumption of the indole; thereby, the yield of the reaction enhanced to 95% with a higher loading of the catalyst (entry 14).

The high-yield and the high regioselectivity of the transformation highlight the reaction to be a new method for the carbazole assembly with diverse functional groups through the designation of different reactants. First, a series of ketones were tested to probe the generality of the annulation (Scheme 3).

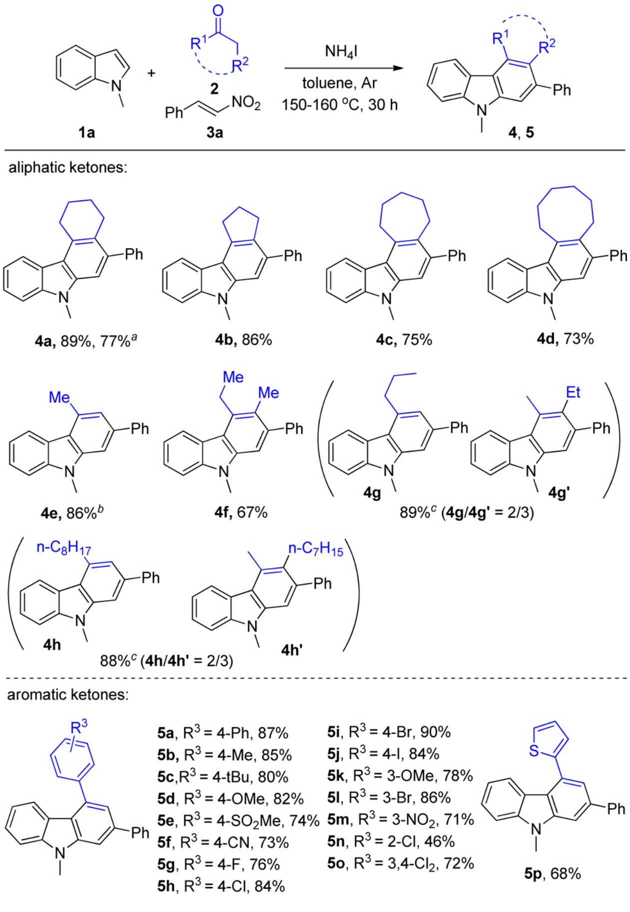
Table 1. Screening the Reaction Conditions[a]



entry	catalyst[b]	atmosphere	temp (°C)	yield[c] (%)
1	DPEphos	air	140	30
2	X-phos	air	140	24
3	Ph_3P	air	140	ND
4	DMAP	air	140	ND
5	1,10-Phen	air	140	ND
6	NH_4I	air	140	58
7	I_2	air	140	21
8	KI	air	140	9
9	$(Me)_4NI$	air	140	ND
10	NH_4I	Ar	140	62
11	NH_4I	O_2	140	30
12	NH_4I	Ar	150	77
13	NH_4I	Ar	160	68
14[d]	NH_4I	Ar	150	95

[a] General conditions: **1a** (0.2 mmol), **2a** (0.2 mmol, 1.0 equiv), **3a** (0.2 mmol, 1.0 equiv), catalyst (0.02 mmol, 10 mol %), toluene (0.5 mL, sealed tube), 30 h. [b] Abbreviations: DPEphos = bis[(2-diphenylphosphino)phenyl] ether; X-phos = 2-(dicyclohexylphosphino)-2′,4′,6′-triisopropylbiphenyl; DMAP = *N,N*-dimethylpyridin-4-amine; 1,10-Phen = 1,10-phenanthroline. [c] Reported yields are determined by GC analysis using dodecane as the internal standard. [d] Catalyst (0.04 mmol, 20 mol %) and **2a** (0.6 mmol, 3.0 equiv) were used. ND = not detected.

Scheme 3. Various Ketones for the Carbazole formation



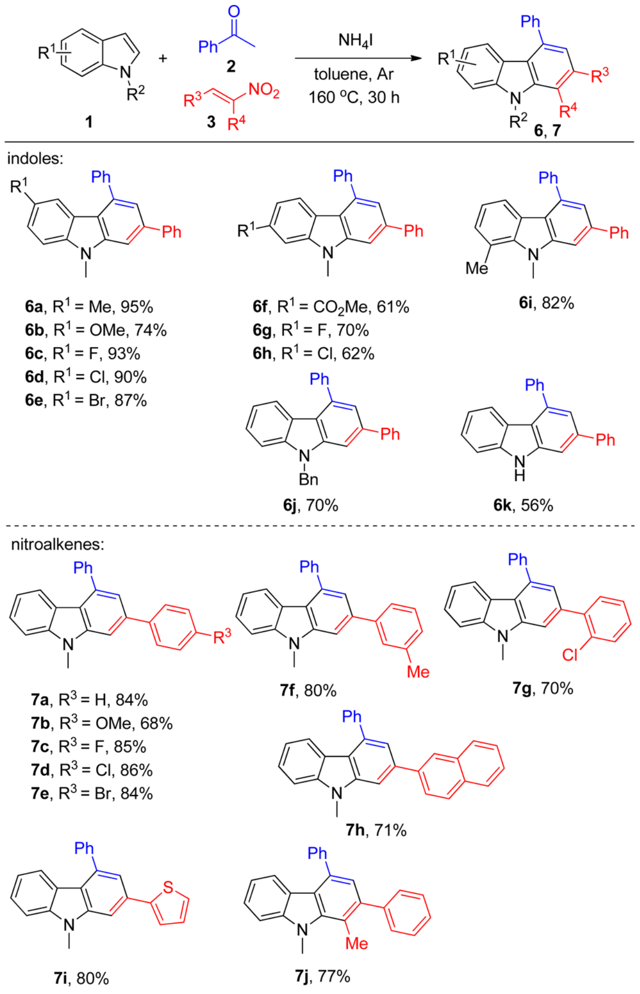
[a] Reaction on a 20 mmol scale. [b] Using 5 equiv of acetone. [c] The yield of two isomers.

Cycloketones such as cyclopentanone, cycloheptanone, and cyclooctanone were also tolerated well in this system (**4b–d**). Excessive acetone seemed essential for a complete conversion of indole and furnished the corresponding products in excellent yield. Acycloketones acetone and pentan-3-one were compatible as well (**4e,f**). Pentan-2-one and decan-2-one as unsymmetrical ketones delivered two isomers of the carbazole products in good overall yield with 3:2 regioselectivity (**4g,h**).

Then we subjected a range of acetylarenes to the present system. A broad range of functional groups on the benzene ring were tolerated well such as methylsulfonyl, nitrile, chloro, bromo, iodo, and nitro group, affording the corresponding products in good to excellent yields (**5a−j**). The steric effect of the substituent was obvious since 1-(2-chlorophenyl)ethanone gave a moderate yield of the carbazole **5n** (versus **5h** (4-Cl) 84% yield). Then we found that 1-(thiophene-2-yl)ethanone reacted well in the annulation and gave a good yield of the desired thiophenyl carbazole **5p**.

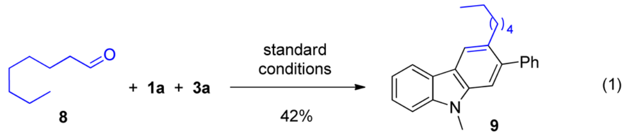
Subsequently, a wide range of substituted indoles were screened to couple with acetophenone and **3a** (Scheme 4).

Scheme 4. Various Indoles and Nitrovinylarenes for the Carbazole Formation

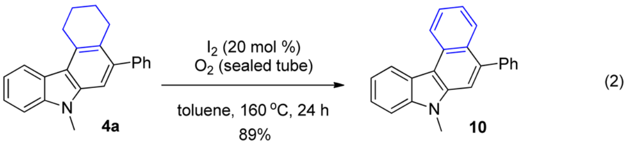


While 1,5-dimethyl-1*H*-indole afforded the corresponding **6a** in 95% yield, both the reactants with electron-donating −OMe (**6b**) and electron-withdrawing $-CO_2Me$ (**6f**) decreased the yield to 74% and 61% yield, respectively. The indoles with halogen −F, −Cl, and −Br were all accommodated well and furnished the desired products in good to excellent yields (**6c−e,g,h**). Then we found the *N*-benzylindole afforded the respective product **6j** in 70% yield and unprotected 1*H*-indole decreased the yield of the transformation to 56% (**6k**). When different functional nitrovinylarenes were screened, good yields of the desired adducts were generally obtained (**7a−g**). Naphthyl and thienyl carbazoles were readily prepared in good yields (**7h,i**). Notably, (*Z*)-(2-nitroprop-1-en-1-yl)-benzene reacted well to afford the 1,9-dimethyl-2,4-diphenyl-9*H*-carbazole **7j** in good yield.

When we replaced the ketone component by an aliphatic aldehyde (**8**), moderate yields of the desired products were obtained, with the alkyl substituent at the C3 position of the carbazole ring (eq 1), which further highlights the synthetic flexibility of this indole-to-carbazole method. For the cyclohexanone-derived carbazole **4a**, dehydroaromatization was smoothly realized by the iodine-catalyzed aerobic oxidation, providing benzo[*c*]carbazole product **10** in excellent yield (eq 2).



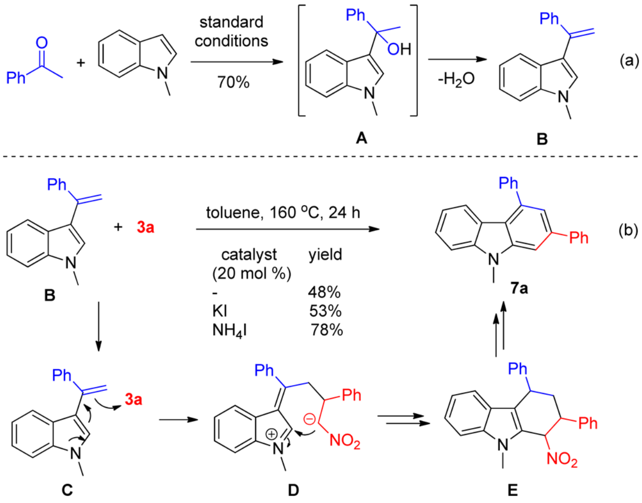
(1)



(2)

Control experiments were conducted to clarify the reaction pathway of the three-component annulation (Scheme 5). First, 3-vinylindole **B** was generated through the combination of ketone and indole under the standard conditions, which undergoes nucleophilic addition of indole to the carbonyl followed by the elimination of H_2O (Scheme 5a).[7a,b] In contrast, NH_4Cl, a second amine such as piperidine and proline, a Lewis acid such as $AlCl_3$, and boron trifluoride−ether did not promote this procedure, and only trace of **B** was observed when acetic acid was used (see the Supporting Information). These observations revealed that the formation of **B** would not proceed through a Friedel−Crafts reaction. In addition, vinylindole readily coupled with nitroalkene **3a** to furnish the final carbazole product even in the absence of catalyst (Scheme 5b). We proposed a Michael-type addition followed by nucleophilic annulation to give tetrahydrocarbazole intermediate **E**. A Diels−Alder process is also possible. Then, the elimination of nitro group releasing nitrous acid and

Scheme 5. Control Experiments



subsequent aromatization formed carbazole product (Scheme 5b).[8]

In summary, we have developed a highly efficient method for carbazole formation through the three-component assembly of indoles, ketones, and nitroalkenes under metal-free conditions. This indole-to-carbazole protocol was demonstrated by the preparation of a broad range of functionalized carbazoles in moderate to excellent yields and features advantages including easily available starting materials, metal-free conditions, high regioselectivity, and wide functional group tolerance. Mechanistic studies indicate a condensation/nucleophilic annulation/aromatization cascade, in which 3-vinylindole is involved as the key intermediate. Further studies on the detailed mechanism and synthetic application are currently underway.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02762.

> Experimental procedures, characterization data for all new compounds, and X-ray crystallographic data for compound **4a** (PDF)

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Notes

The authors declare no competing financial interest.

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