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# Benzannulation of Indoles to Carbazoles and Its Applications for Syntheses of Carbazole Alkaloids

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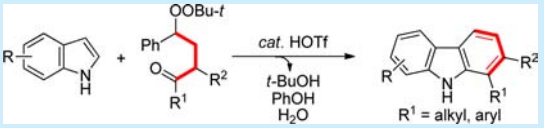
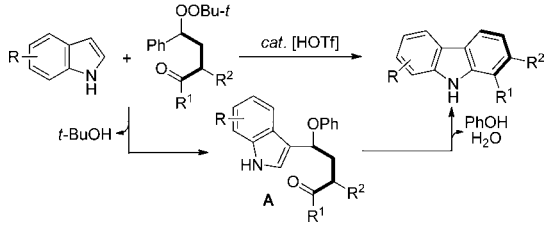
Supporting Information

**ABSTRACT:** A novel and efficient method for the benzannulation of indoles to carbazoles is reported. γ-Carbonyl *tert*-butylperoxide is applied as a new diene building block for the π-extension of simple indoles. The synthetic utility of this method is demonstrated by concise and selective total syntheses of naturally occurring carbazole alkaloids, olivacine, and asteropusazole A.



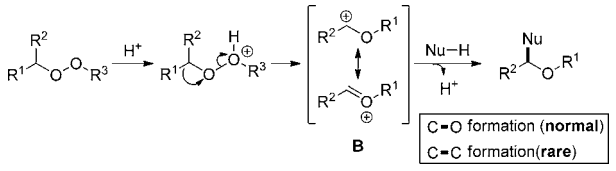

Carbazole alkaloids are found in diverse natural sources, and many of them display a broad range of biological activities. Carbazole scaffolds are also useful building blocks for a variety of organic materials. Tremendous efforts have been made to synthesize structurally diverse and biologically active carbazole compounds.[1] Direct conversion of indoles into carbazoles has high synthetic potential because indoles are readily available and easily prepared. Alkenes,[2] alkynes,[3] dicarbonyls,[4] and others[5] have been successfully used as diene precursors for the construction of a carbazole skeleton from simple indoles. However, the synthetic utility of these reactions for the synthesis of bioactive natural carbazoles is virtually unknown due to limitations of the substrate scope.[6] In this regard, the discovery of versatile diene precursors poses a key challenge for the development of the indole-to-carbazole approach. We now demonstrate that γ-carbonyl *tert*-butylperoxides can be used as a new diene building block to allow direct benzannulation of simple indoles through an acid-catalyzed rearrangement of *tert*-butylperoxide (Scheme 1). Concise syntheses of olivacine and asteropusazole A have been achieved by using this method, highlighting the advantages of the protocol.

**Scheme 1. Benzannulation of Indoles to Carbazoles**




The peroxide chemistry has received considerable attention ranging from natural occurring peroxides[7] to unconventional intermediates[8] in synthetic chemistry. For example, Dussault[9] and we[10] demonstrated complementarily a new strategy to synthesize cyclic ethers via intramolecular nucleophilic cyclization of dialkyl peroxides in the presence of base. On the other hand, the acid-catalyzed (Hock) rearrangement of organic peroxides has been extensively investigated in both biochemistry, which is related to the oxidative degradation of organic molecules especially lipids, and synthetic chemistry such as cumeme process. The key oxycarbenium ion intermediate **B**, generated by the migration of a neighboring substituent, is normally attacked by $H_2O$ thus leading to hemiacetal (Scheme 2), which cleaves to give the final products.

**Scheme 2. Acid-Catalyzed Rearrangement of Peroxide**




We envisioned that α-substituted ethers might be obtained if **B** is trapped by other nucleophiles such as indoles, pyrroles, and phenols. However, C−C bond formation through Hock cleavage is still a distinct challenge.[11]

To verify our hypothesis, we examined the reactions of γ-carbonyl *tert*-butylperoxides with a variety of nucleophiles. To our surprise, carbazoles were obtained when indole was used as nucleophile, indicating that **A** in Scheme 1 is generated as a key intermediate for carbazole formation. Accordingly, we chose indole **1a** and peroxide **2a** as standard substrates to investigate suitable reaction conditions (Table 1). The efficiency of the carbazole formation strongly depended on the acidity of the acids (entries 1−3) and solvent (entries 4−7). It should be noted that carbazole **3a** was not observed and the starting materials remained in the absence of acid (entry 8).

The generality of this transformation was briefly investigated under the optimized reaction conditions (Figure 1). To our satisfaction, a variety of indoles **1** reacted smoothly with γ-carbonyl *tert*-butylperoxides **2**, which were easily prepared by

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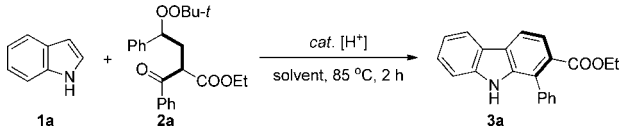
**Table 1. Optimization of Reaction Conditions**[a]




| entry | [H+] | 1a (x equiv) | solvent | yield (%)[b] |
|---|---|---|---|---|
| 1 | TFA | 1.0 | MeCN | 5 |
| 2 | TsOH·$H_2O$ | 1.0 | MeCN | 18 |
| 3 | TfOH | 1.0 | MeCN | 62 |
| **4** | **TfOH** | **1.2** | **MeCN** | **76(65)** |
| 5 | TfOH | 1.2 | toluene | 14 |
| 6 | TfOH | 1.2 | dioxane | 25 |
| 7 | TfOH | 1.2 | HOAc | 43 |
| 8 | – | 1.2 | MeCN | NR[c] |

[a]Reaction conditions: **2a** (0.2 mmol), [H+] (0.1 mmol), solvent (2.0 mL). [b]NMR yields were determined by $^1$H NMR using an internal standard (isolated yield in parentheses). [c]No reaction.

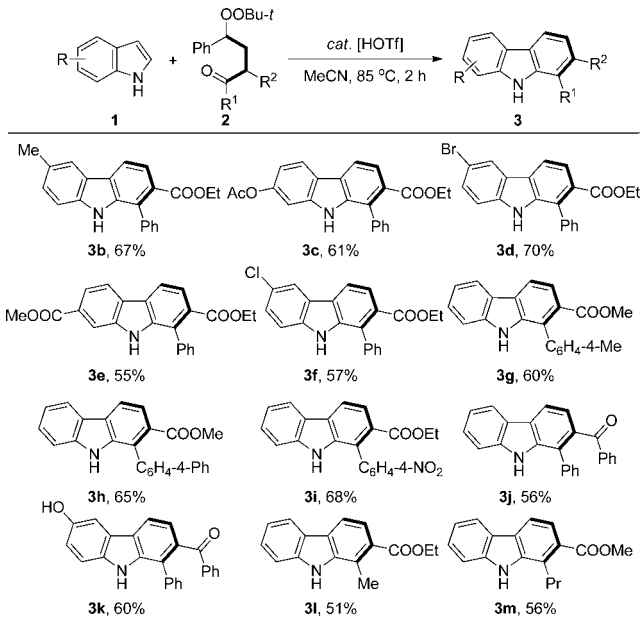
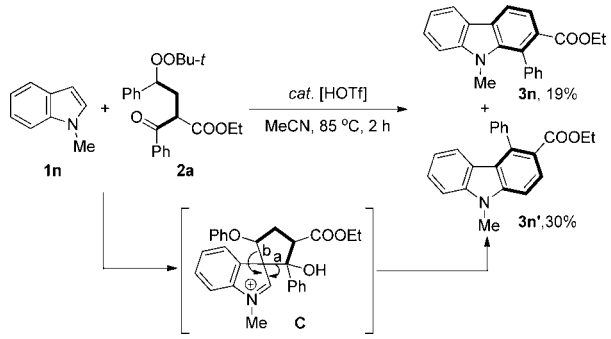



**Figure 1.** Examples for indole-to-carbazole: **1** (0.24 mmol), **2** (0.2 mmol), TfOH (0.1 mmol), MeCN (2.0 mL).

three-component reactions of styrene, 1,3-dicarbonyls, and *tert*-butyl hydroperoxide (TBHP).[12] Multisubstituted carbazoles **3** bearing functional groups were synthesized efficiently through this indole-to-carbazole approach.

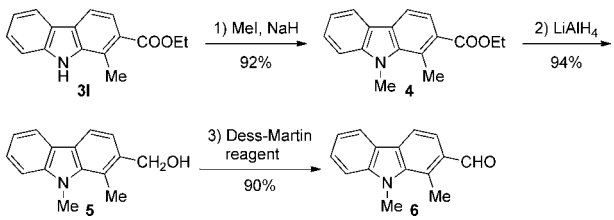
When *N*-methylindole **1n** was used, two regioisomeric carbazoles **3n** and **3n′** were obtained (Scheme 3). This result indicated that a spiro iminium intermediate **C** was likely generated in situ and underwent two different 1,2-alkyl migrations,[5d,13] thus leading to two regioisomers. It should be noted that the other isomeric carbazoles **3′** were not obtained when $R^1$ of **2** are aromatic groups, but trace amounts (<5%) of isomeric carbazoles **3l′** and **3m′** were observed by the crude $^1$H NMR spectra of the resulting reaction mixtures (Figure 1).[14] We hypothesized that the migration of tertiary carbon (route a) to give **3** is predominant for (*N*-H)-indoles (Figure 1),[15] while the steric effect caused by the *N*-methyl group of indole **1n** leads to the migration of secondary carbon (route b) to give **3n′** as the major product (Scheme 3).

**Scheme 3. Reaction of *N*-Methyl Indole 1n with 2a**




To synthesize *N*-methyl carbazoles, methylation of *N*-H carbazoles will provide an alternative route to avoid the regioselectivity problem of the present method. For example, methylation of **3l** with MeI in the presence of NaH afforded **4** in 92% yield (Scheme 4). Reduction of **4** followed by oxidation

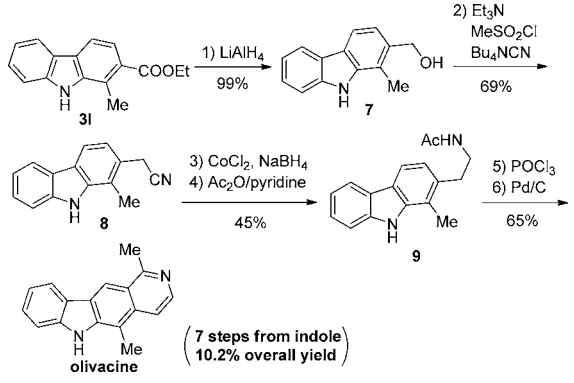
**Scheme 4. Synthesis of *N*-Methyl Carbazoles**




of the terminal alcohol led to 1,9-dimethyl-9*H*-carbazole-2-carbaldehyde **6** efficiently, which was applied as the key precursor for synthesis of *N*-methyl pyrido[4,3-*b*]carbazole alkaloids.[16]

Olivacine as a member of pyrido[4,3-*b*]carbazole alkaloids was first isolated from *Aspidosperma olivaceum* in 1958, and since then, it was also found in many members of the Apocynaceae family.[17] Due to its antitumor activity in several animal and human tumor systems,[18] synthesis of olivacine has attracted much attention. Several methods for the synthesis of olivacine were reported.[19] To demonstrate the synthetic utility of the benzannulation of indole with γ-carbonyl *tert*-butylperoxide, we chose olivacine as a target molecular (Scheme 5). Reduction of the ester group of **3l** by $LiAlH_4$ afforded carbazyl methanol **7** in a quantitative yield. Cyanation followed by reduction and acylation led to carbazyl ethyl acetamide **9**. Intramolecular condensation and subsequent

**Scheme 5. Synthesis of Olivacine**



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catalytic dehydrogenation by Pd/C provided olivacine. The total synthesis was achieved in seven steps from indole with a 10.2% overall yield.

The indolo[3,2-*a*]carbazole skeleton, one of the isomeric indolocarbazoles, was identified for the first time from nature in 2002.[20] Up to now three members of this family were isolated from marine sponges (Figure 2). The preliminary results of the

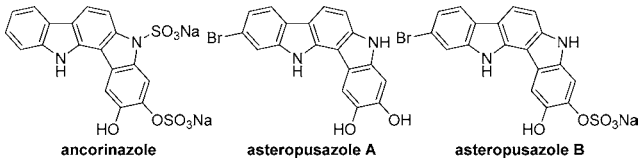
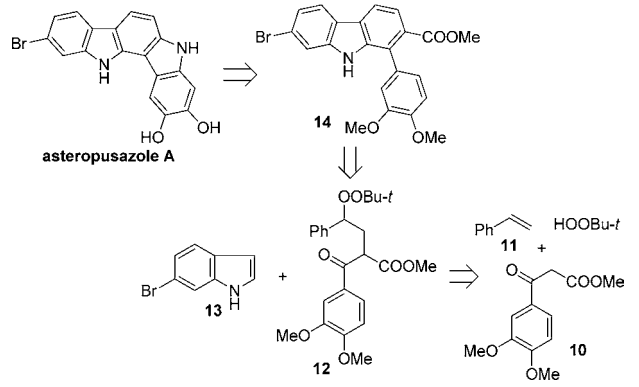



**Figure 2.** Natural indolo[3,2-*a*]carbazole alkaloids.

antimicrobial and cytotoxicity assays indicated that these compounds especially asteropusazole A are medicine candidates to target neurological and psychiatric disorders.[21]

Although a limited number of methods for the construction of the indolo[3,2-*a*]carbazole skeleton were developed,[22] total synthesis of these natural products has not been achieved. Based on the structure analysis, our retrosynthetic route to asteropusazole A is given in Scheme 6. The indole unit of

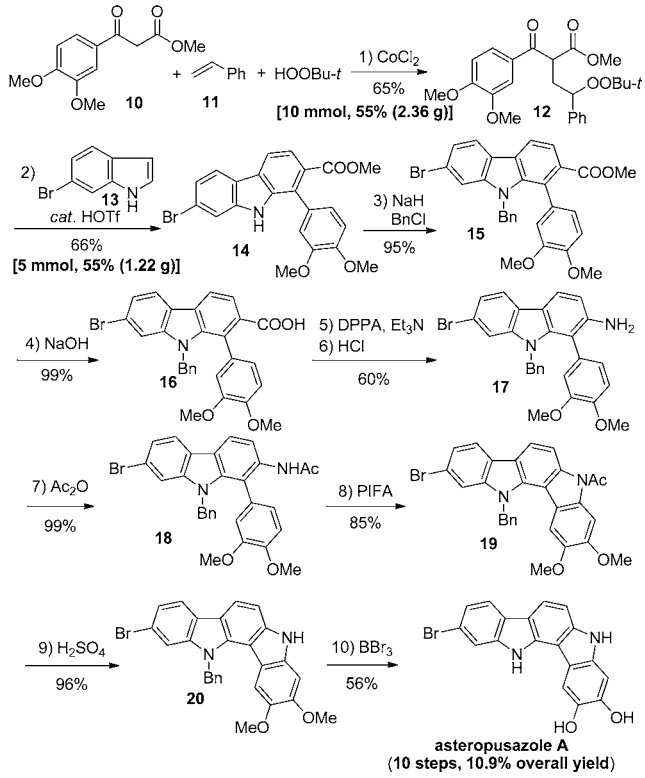
**Scheme 6. Retrosynthetic Analysis for Asteropusazole A**




asteropusazole A can be accessed from the carbazole **14** by the transformations of the ester group. We envisioned that the desired precursor **14** can be synthesized by the benzannulation of 6-bromoindole **13** with *γ*-carbonyl *tert*-butylperoxide **12**, which can be assembled by Co-catalyzed alkylation−peroxidation of styrene **11** with *β*-ketoester **10** and TBHP.

The synthesis of asteropusazole A is summarized in Scheme 7. A $CoCl_2$-catalyzed three-component reaction of *β*-keto ester **10**, styrene **11**, and TBHP gave the corresponding *γ*-carbonyl *tert*-butylperoxide **12** in 65% yield (step 1). Benzannulation of 6-bromoindole **13** with the peroxide **12** smoothly led to the expected carbazole precusor **14** in the presence of TfOH. It should be noted that ethyl acetate instead of MeCN was employed as solvent and increased the yield of **14** to 66% (step 2). The efficiency and selectivity of the synthesis of **14** is quite remarkable: (*i*) the peroxide **12** could be prepared in 10 mmol scale with a synthetically useful yield from simple materials, (*ii*) the carbazole **14** could be also synthesized in gram scale as a single isomer. Due to the lower yield of a later intramolecular cyclization (step 8), protection of (N−H) carbazole **14** was necessary (step 3). Hydrolysis of **15** led to the carbazole carboxylic acid **16** in a quantitative yield (step 4). Curtius

**Scheme 7. Total Synthesis of Asteropusazole A**




rearrangement successfully provided the corresponding amine **17** (steps 5 and 6). Extensive studies[23] revealed that the oxidative cyclization[24] of acetamide **18** to **19** by phenyliodine(III) bis(trifluoroacetate) (PIFA) was an excellent approach for the construction of the indole unit of asteropusazole A (steps 7 and 8). Finally, after deprotections by $H_2SO_4$ (step 9) and $BBr_3$ (step 10), asteropusazole A was successfully obtained for the first time in 10 steps with a 10.9% overall yield.

In conclusion, we have demonstrated a general and practical method for carbazole synthesis through the benzannulation of indoles with *γ*-carbonyl *tert*-butylperoxides. The key step of the approach is based on the acid-catalyzed rearrangement of *tert*-butylperoxides. The indole-to-carbazole strategy was successfully applied for the selective and concise synthesis of olivacine and the first total synthesis of asteropusazole A from simple starting materials. Efforts to expand on the synthesis of structurally diverse *γ*-carbonyl *tert*-butylperoxides and other natural products are underway and will be reported in due course.

## ■ ASSOCIATED CONTENT

### Supporting Information

Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.



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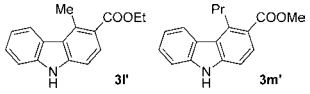
(14) The possible structures of **3l′** and **3m′**:




(15) Alternatively, the initial oxycarbenium derived from Hoch rearrangement might be trapped reversibly by the indole nitrogen to generate an unstable aminal, followed by intramolecular condensation to set up the carbon of ketone at the neighboring carbon (C2).

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