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Facile Synthesis of Fully Substituted Dihydro-β-carbolines via Brønsted Acid Promoted Cascade Reactions of α-Indolyl Propargylic Alcohols with Nitrones

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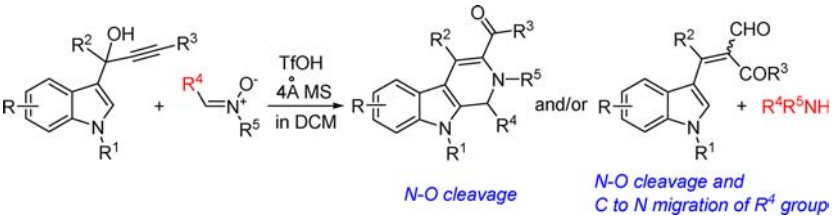
ABSTRACT



A straightforward synthesis of fully substituted β-carbolines via Brønsted acid promoted cyclizations of α-indolyl propargylic alcohols with nitrones is described. The use of nitrones bearing alkenyl or electron-rich aryl groups as the R^4 substituent dramatically switches the reaction pathway to afford tetrasubstituted alkenes and amines, which is assumed to proceed through a rearrangement reaction involving N−O bond cleavage and 1,2-migration of the R^4 group to an adjacent nitrogen atom.

β-Carbolines, including its reduced derivatives, represent a large group of biologically active indole alkaloids widespread in nature.[1] For example, Jadiffine[2] and Neonaucleoside C[3] were isolated from *Vinca difformis* and *Neonauclea sessilifolia*, respectively. Lavendamycin is a naturally occurring antitumor antibiotic, which possesses cytotoxic properties and exhibits significant activity against topoisomerases (Figure 1).[4] β-Carbolines also act as useful intermediates for natural product synthesis.[5] As a consequence, much attention has been paid to the synthesis of β-carboline derivatives.[6] The most common strategy is through the Pictet−Spengler reaction.[7] Others include, for examples, ring derivatizations,[8] metal or Lewis acid catalyzed intramolecular nucleophilic cyclization at the

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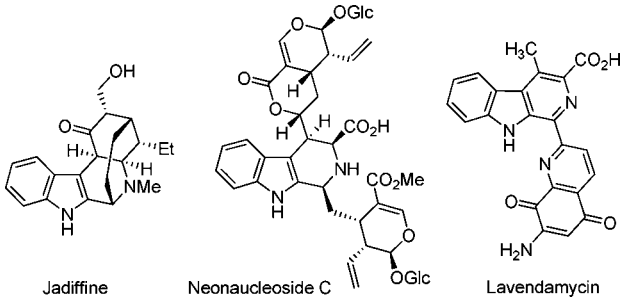


Figure 1. Representative examples of highly substituted β-carboline alkaloids.

C-3 position of indole,[9] copper-catalyzed C−N bond coupling reactions,[10] Ru-catalyzed [2 + 2 + 2] cycloaddition of an electron-deficient nitrile to an alkynylynamide,[11] etc. Nevertheless, the development of straightforward methodology that allows the formation of densely substituted β-carbolines still remains an important objective. We have recently reported a series of gold-catalyzed cascade transformations of indolyl tethered alkynes,[12] such as cascade Friedel−Crafts/hydroarylation of indoles with (*Z*)-enynols,[12a] 1,5-indole migration reactions,[12b] and deacylative cycloisomerization of 3-acylindole/ynes[12c] into carbazole derivatives. On the other hand, recent research demonstrated that nitrones could serve as a satisfactory oxidant for redox reactions with cleavage of a weak N−O bond in gold-catalyzed reactions, leading to an oxygen-atom transfer to alkynes.[13] We envisioned that the use of nitrone as a nucleophile to attack the alkyne moiety of indole/ynes might initialize new types of cascade reactions. Along this line, we discovered that fully substituted dihydro-β-carbolines could be constructed conveniently via tandem reactions of α-indolyl propargylic alcohols with nitrones promoted by Lewis or Brønsted acids (Scheme 1). Herein we'd like to describe this new protocol to β-carbolines.

Scheme 1. A New Strategy for the Synthesis of Dihydro-β-carbolines

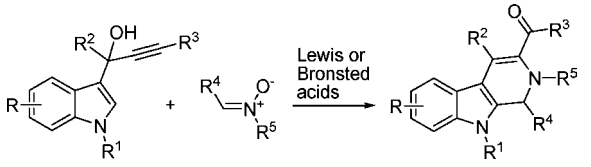
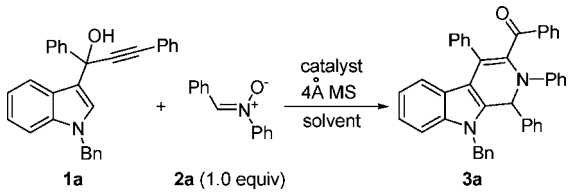
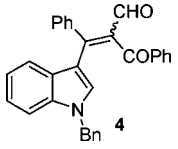


Table 1. Optimization of Reaction Conditions



entry	catalyst (equiv)	solvent	temp (°C)	time	yield(%)[a]
1	$Ph_3PAuNTf_2$ (0.05)	CH_3NO_2	100	4 h	40
2	$Ph_3PAuNTf_2$ (0.05)	CH_3NO_2	150	4 h	24
3	$Sc(OTf)_3$ (0.2)	CH_3NO_2	0	15 min	59
4	$Sc(OTf)_3$ (0.3)	CH_3NO_2	0	15 min	62
5	$Sc(OTf)_3$ (0.5)	CH_3NO_2	0	15 min	69
6	TfOH (1.0)	CH_3NO_2	0	15 min	61
7	TfOH (1.0)	DCM	0	15 min	66[b]
8	TfOH (0.5)	DCM	0	15 min	57[c]
9	TfOH (1.0)	DCM	0	15 min	55[d]
10	$TsOH·H_2O$ (1.0)	DCM	0	15 min	trace
11	MsOH (1.0)	DCM	0	15 min	18
12	CF_3COOH (1.0)	DCM	0	15 min	-[e]

[a] Isolated yields. [b] Compound **4** was also isolated in 18% yield as a mixture of two isomers in the ratio of 2.4:1. [c] **4** was isolated in 15% yield as a mixture of two isomers in the ratio of 2.4:1. [d] In the absence of molecular sieve. [e] Complicated reaction mixture.



In light of the efficient activation of alkynes by gold catalysts, we first investigated the model reaction of the propargylic alcohol **1a** with nitrone **2a** in the presence of 5 mol % of PPh_3AuNTf_2 (Table 1).[14,15] It was found that β-carboline **3a** could be obtained in 40% yield at 100 °C in CH_3NO_2 (Table 1, entry 1). Elevating the reaction temperature to 150 °C did not improve the reaction, and **3a** was isolated in 24% yield (entry 2). Advantageously, the use of 30 mol % of $Sc(OTf)_3$ could enable the reaction to proceed at 0 °C and improve the yield of **3a** to 62% (entry 4). Decreasing or increasing the amounts of the

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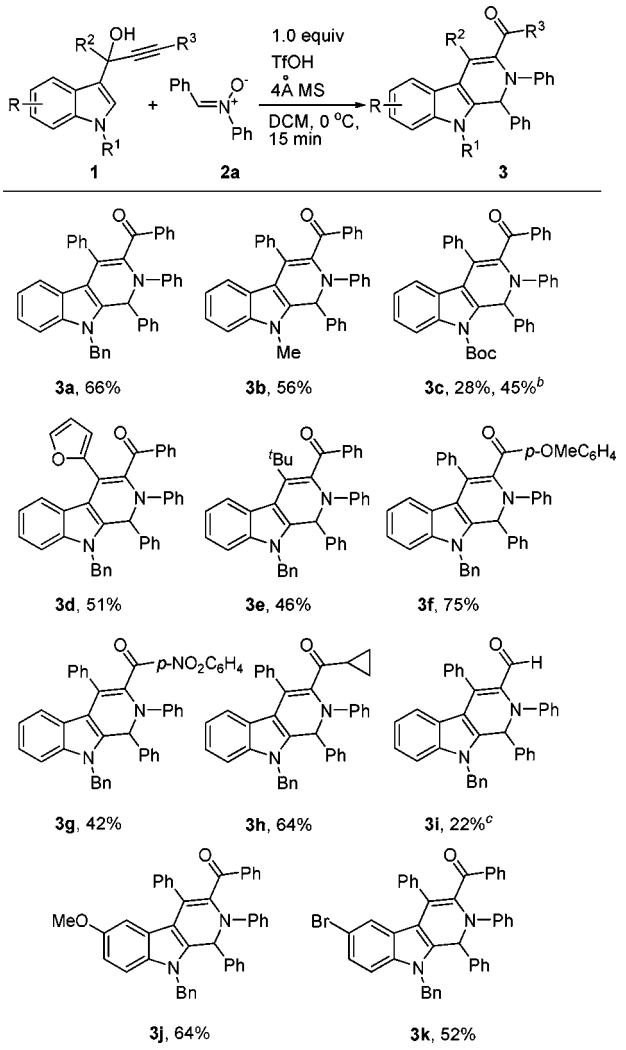
Scheme 2. Scope of Propargylic Alcohols[a]

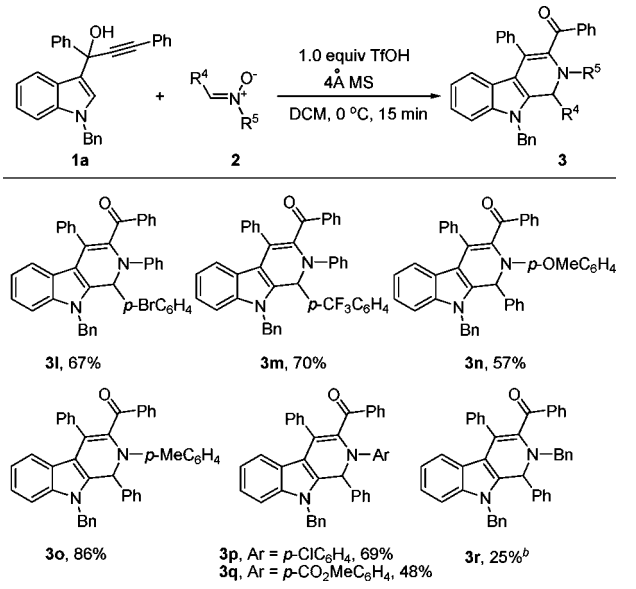


[a] Isolated yields. [b]30% $Sc(OTf)_3$, 4Å MS, in CH_3NO_3, rt, 15 min. [c]1 h.

catalyst did not change the product yields significantly (entries 3 and 5). Further studies revealed that the conjugate acid of the metal triflates, TfOH, also showed good activities to afford 61% of **3a** in CH_3NO_2 or 66% of **3a** in DCM (entries 6–7). In the latter case, a tetrasubstituted alkene with two electron-withdrawing groups **4** was also isolated in 18% yield. A catalytic amount (50 mol %) of TfOH afforded a lower yield of **3a** (57%, entry 8). In the absence of molecular sieve, **3a** was obtained in a lower yield of 55% (entry 9). Other Brønsted acids, such as $TsOH \cdot H_2O$, MsOH, or CF_3COOH, were less or not effective (entries 10–12). We chose Table 1, entry 7 as the optimum conditions due to the lower cost of TfOH.

Having the optimized reaction conditions in hand, we next examined the substrate scope with a range of α-indolyl-bearing propargylic alcohols. As shown in Scheme 2, a wide range of propargylic alcohols could be converted into the desired β-carbolines in the presence of 1.0 equiv of TfOH. The use of *N*-methyl-substituted indole afforded the corresponding carboline **3b** in 56% yield.

Scheme 3. Scope of Nitrones[a]



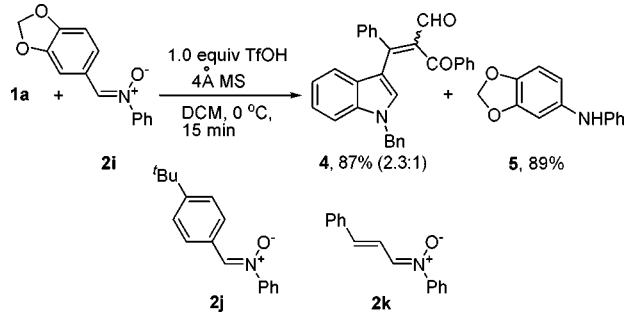
[a] Isolated yields. [b]Room temperature, 3 h.

However, an *N*-Boc-protected substrate gave the product **3c** in a low yield of 28%, possibly due to the instability of the starting alcohol **1c** under the acidic conditions. The use of $Sc(OTf)_3$ as a catalyst could improve the yield of **3c** to 45%. A heteroaryl group such as 2-furanyl as the R^2 substituent afforded 51% of **3d**. Alkyl substitution as R^2 as in the case of ^{t}Bu-substituted substrate **1e** also worked smoothly to give **3e** in 46% yield. Next, we investigated the substituent effects on the alkyne terminus (R^3 group). Both electron-rich (p-$MeOC_6H_4$) and electron-poor (p-$NO_2C_6H_4$) aryl substituents were tolerated, furnishing the corresponding β-carbolines **3f** and **3g** in 75% and 42% yields, respectively. The results indicated that the electron-withdrawing substituent on the aryl ring led to a lower yield of the product, which might be due to the lower stability of the allenyl cation intermediate formed in the initial step. A cyclopropyl-group as R^3 was also suitable in this domino reaction, producing **3h** in 64% yield. However, a terminal alkyne only led to a 22% yield of **3i**. 5-MeO or 5-Br-substituted indole substrates were also compatible for this transformation to deliver **3j**–**3k** in 52–64% yields. The structure of **3** was unambiguously confirmed by X-ray single-crystal analysis of **3b** and **3c**.[16]

The scope of nitrones was also tested using **1a** as a reaction partner (Scheme 3). It was found that, for nitrones bearing electron-deficient *C*-aryl groups (R^4), such as the p-BrC_6H_4 or p-$CF_3C_6H_4$ group, the desired carbolines **3l**–**3m** could be obtained in 67–70% yields. However, when R^4 is an electron-rich aryl group, product **4** was isolated as a major product (*vide infra*). The *N*-aryl rings bearing p-MeO, p-Me, p-Cl, and p-CO_2Me substituents reacted smoothly with **1a** to afford **3n**–**3q** in 48–86% yields. The use of *N*-Bn-substituted nitrone gave a low yield of **3r**.

(16) See Supporting Information.

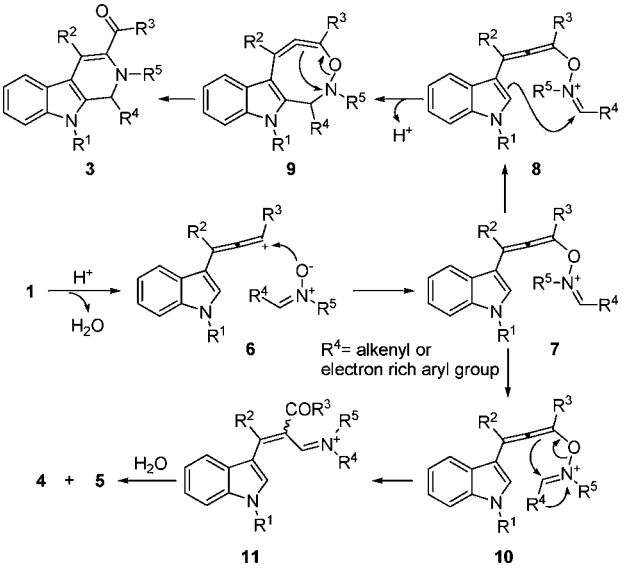
Scheme 4. 1,2-Migration Reactions



As mentioned above, when nitrones bearing an electron-rich *C*-aryl group was employed, product **4** was isolated as a major product. For example, when **1a** was reacted with nitrone **2i** substituted with a strong electron-donating methylenedioxy group on the *C*-aryl ring, **4** was formed in 87% yield, and an unexpected liberation of *N*-phenylbenzo-[*d*][1,3]dioxol-5-amine **5** was also observed (Scheme 4). The results indicated that the migration of a *C*-aryl group to the nitrogen atom occurred during the reaction. Similarly, the use of nitrone **2j** (R^4 = *p*-^{t}BuC$_6$H$_4$) and **2k** (R^4 = —CH=CH—Ph) resulted in the formation of **4** in 83% and 86% yields, respectively. The structure of **4** was confirmed by X-ray single-crystal analysis.[16]

Based on the above observations and the known precedents in literature, we propose the following reaction mechanism for this reaction (Scheme 5). Initially, allenyl cation **6** is generated via a Meyer–Schuster rearrangement,[17,18] which is attacked by nitrone **2** to give intermediate **7**. **7** undergoes cyclization via attack of the indolyl moiety to the iminium cation leading to eight-membered N–O heterocycle **9**. 1,3-Rearrangement of **9** with cleavage of the N–O bond, similar to Baldwin rearrangement and related reactions,[19] delivers highly substituted *β*-carboline **3**. When R^4 is an alkenyl or electron-donating aryl group, cleavage of the N–O bond from **7** is accompanied by the migration of the R^4 group to the nitrogen atom[20] to give iminium ion **11**. Hydrolysis of **11** affords the alkene product **4** and releases the amine **5**. The results also demonstrate that the electron-rich *π*-system tends toward migration.[20]

Scheme 5. Possible Reaction Mechanism



In summary, we have developed a new procedure for the synthesis of fully substituted 1,2-dihydro-*β*-carbolines via Brønsted acid mediated cyclization of α-indolyl propargylic alcohols with nitrones. The use of nitrones bearing an electron-rich *C*-aryl ring or *C*-alkenyl group dramatically switches the reaction pathway to afford tetrasubstituted alkenes and amines, which is assumed to proceed through a rearrangement reaction involving N–O bond cleavage and 1,2-migration. These results will be of importance for the development of new reactions with the use of nitrones. Clarification of the reaction mechanism and further application of this chemistry are in progress.

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Supporting Information Available. Experimental details, spectroscopic characterization of all new compounds, and X-ray crystallography of compounds **3b**, **3c** and **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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