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Synthesis of 1*H*-Pyrrolo[1,2-*a*]indoles *via* Lewis Acid-Catalyzed Annulation of Propargylic Alcohols with 2-Ethynylanilines

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Abstract. A novel highly efficient, environmentally benign Lewis acid-catalyzed, and protection-free protocol for the construction of valuable polycyclic products bearing a 1*H*-pyrrolo[1,2-*a*]indole scaffold is described, starting from readily available propargylic alcohols and 2-ethynylanilines. The one-pot transformation entails the cleavage of one C-O bond, and the construction of two *C-N* bonds and one C-C double bond. This unique operationally simple method is performed under mild conditions and in air, producing water as the only byproduct; it is scalable and demonstrates good functional group compatibility and broad scope.

Keywords: 1*H*-pyrrolo[1,2-*a*]indole derivatives; Lewis acid-catalyzed; propargylic alcohols; 2-ethynylanilines; nucleophilic addition

A major challenge in modern organic synthetic chemistry is the development of synthetically useful methods for the strategically efficient and selective assembly of complex heterocycles, carbocycles and condensed molecular structures from readily accessible starting materials.[1-2] Tandem reaction processes incorporating multistep reactions into a single one pot procedure provide elegant routes to complex carbon or hetero frameworks from relatively simple precursors, thus highlighting the fundamental demands of an "ideal synthesis".[3] Over the past few decades, significant research efforts have been devoted to developing organic synthetic methodology focused on environmentally benign, atom-economical, operational simplicity pathways, taking into account the purpose of "green environmental protection and sustainability". Propargyl alcohols and their derivatives, bearing alkynyl and hydroxyl (ester) functional groups, have become increasingly important starting materials and have been extensively used as building blocks for the synthesis of functional materials, pharmaceuticals, and bioactive compounds.[4] In particular, cascade annulations of propargyl alcohols and their derivatives catalyzed by Lewis and Brønsted acids, as well as halogenation reagents, have provided a versatile and powerful tool for the construction of a broad variety of highly functionalized complex carbocyclic and heterocyclic scaffolds. These types of motifs are valuable starting points and are abundant in biologically active natural products and functional materials.[5]

Polycyclic indoles represent an important class of fused heterocycles, and are the core structural motifs of a wide array of agrochemicals and pharmaceuticals. Among them, 1*H*-pyrrolo[1,2-*a*]indoles are of great interest in organic synthesis and medicinal chemistry due to their significant biological and pharmacological activities, such as antitumor, antimalarial, antiviral, and anti-implantation activities.[6] For example, a novel alkaloid isatisine A, isolated from the leaves of *Isatis indigotica* Fort, used in traditional Chinese medicine, exhibits inhibitory activities against viral diseases including viral pneumonia, influenza, and hepatitis.[7] Mitomycin C, belonging to the family of antitumor antibiotics isolated from *Streptomyces caespitosus* was identified as a clinical agent for the treatment of a series of solid tumors.[8] 5-Hydroxytryptamine, as a critical neurotransmitter, participates in a broad variety of motor, sensory, and behavioral processes.[9]

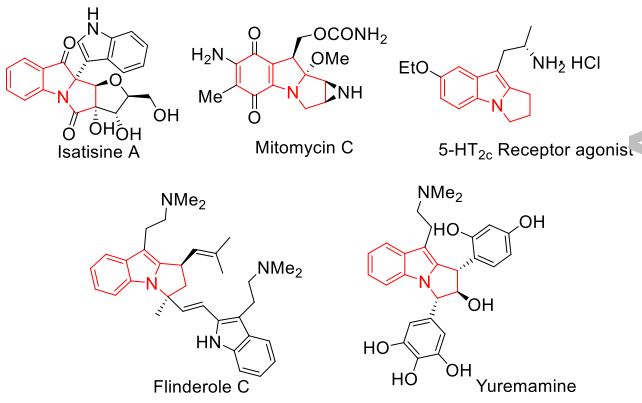

Figure 1. Selected examples bearing the 1*H*-pyrrolo[1,2-*a*]indole scaffold

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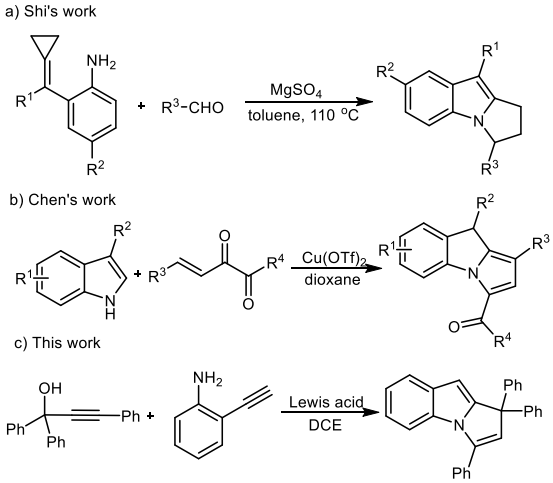
Scheme 1. Summary of the previous and current studies towards the 1*H*-pyrrolo[1,2-*a*]indole scaffold

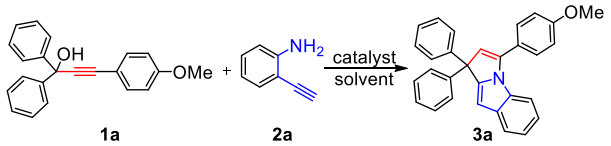


Flinderole C containing a unique rearranged skeleton isolated from the Papua New Guinean plant *F. amboinensis* is one of the most selective and effective known inhibitors against malaria.[10] Yuremamine, an alkaloid isolated from the stem bark of *Mimosa hostilis*, was identified as having the ability to treat burns and other skin afflictions, and has hallucinogenic and psychoactive effects.[11]

Due to the critical importance and ubiquity of this framework in organic and medicinal chemistry, the development of facile and efficient tandem procedures and alternative methods to access the 1*H*-pyrrolo[1,2-*a*]indole structural motif from easily prepared starting materials is particularly desirable.[12] In 2012, the Shi group reported a magnesium-catalyzed cascade reaction of aniline-tethered alkylidenecyclopropanes and aldehydes for the construction of functionalized pyrrolo[1,2-*a*]indoles (Scheme 1a).[13] Recently, a facile copper(II) trifluoromethanesulfonate-catalyzed Friedel−Crafts alkylation/annulation cascade reaction for the synthesis of diverse 9*H*-pyrrolo[1,2-*a*]indoles, employing substituted indoles and 1,2-dicarbonyl-3-enes as the substrates, has been developed by the Chen group (Scheme 1b).[14] These intriguing discoveries have stimulated our interest in exploring new synthetic strategies for accessing these compounds. Herein, we report an unprecedented copper(II) trifluoromethanesulfonate-catalyzed cascade cyclization of propargylic alcohols and 2-ethynylanilines as a facile, highly efficient, and atom-economical synthesis of 1*H*-pyrrolo[1,2-*a*]indole derivatives under mild conditions.

The initial conditions entailed propargylic alcohol **1a** (0.1 mmol) as the model substrate reacting with 2-ethynylaniline **2a** (0.2 mmol) in the presence of commonly used $Zn(OTf)_2$ (20 mol %) in DCE at 40 °C for 4 h under an air atmosphere (Table 1, entry 1). Gratifyingly, the desired product **3a** was detected and obtained in 52% yield, and its molecular structure was explicitly established by X-ray crystallographic

Table 1. Optimization of the Reaction Conditions of **1a** with 2-Ethynylaniline[a, b]



1a **2a** **3a**

entry	catalyst (mol %)	solvent	temp (°C)	t (h)	yield (%)[b]
1	$Zn(OTf)_2$ (20)	DCE	40	4	52%
2	$Al(OTf)_3$ (20)	DCE	40	4	54%
3	$Y(OTf)_3$ (20)	DCE	40	4	19%
4	AgOTf (20)	DCE	40	4	61%
5	$Yb(OTf)_3$ (20)	DCE	40	4	14%
6	$Cu(OTf)_2$ (20)	DCE	40	4	64%
7	$Cu(OTf)_2$ (20)	DCE	50	4	69%
8	$Cu(OTf)_2$ (20)	DCE	60	4	70%
9	$Cu(OTf)_2$ (20)	DCE	70	4	73%
10	$Cu(OTf)_2$ (20)	DCE	80	4	81%
11	$Cu(OTf)_2$ (20)	DCE	80	6	87%
12	$Cu(OTf)_2$ (20)	DCE	80	8	83%
13	$Cu(OTf)_2$ (20)	DCE	80	10	80%
14	**$Cu(OTf)_2$ (15)**	**DCE**	**80**	**6**	**81%**
15	$Cu(OTf)_2$ (10)	DCE	80	6	72%
16	$Cu(OTf)_2$ (15)	THF	80	6	11%
17	$Cu(OTf)_2$ (15)	CH_3CN	80	6	trace
18	$Cu(OTf)_2$ (15)	toluene	80	6	trace
19	$Cu(OTf)_2$ (15)	1,4-dioxane	80	6	trace

[a] Unless otherwise noted, all reactions were performed with **1a** (0.1 mmol) and 2-ethynylaniline **2a** (2.0 equiv) in solvent (2.0 mL). [b] Yields are given for isolated products.

analysis and NMR spectroscopy (see the Supporting Information)[15]. Among the various Lewis acid catalysts evaluated for this transformation, $Cu(OTf)_2$ exhibited superior catalytic activity, increasing the product yield to 64% (entries 2-6). A subsequent adjustment in the reaction temperature revealed that the reaction attained its highest catalytic activity for the production of **3a** at 80 °C (entries 7-10). The yield was further improved to 87% by prolonging the reaction time to 6 h (entry 11). Moreover, lowering the catalyst loading to 15 mol % led to a slightly diminished yield. (entries 14-15). A brief evaluation of several representative solvents, such as THF, CH_3CN, toluene, and 1,4-dioxane indicated that DCE was the optimal solvent. Ultimately, the optimal reaction conditions were determined to be: alkynol substrate **1a** (0.1 mmol) and 2-ethynylaniline **2a** (2.0 equiv), in the presence of $Cu(OTf)_2$ (15 mol %) in DCE (2.0 mL) at 80 °C for 6 h under an air atmosphere.

With the optimal conditions in hand, the scope of the propargylic alcohols was evaluated next and the results are depicted in Scheme 2. A wide variety of aryl(hetero)-substituted propargyl alcohols bearing electron-rich or electron-deficient substituents coupled smoothly with 2-ethynylaniline **2a**,

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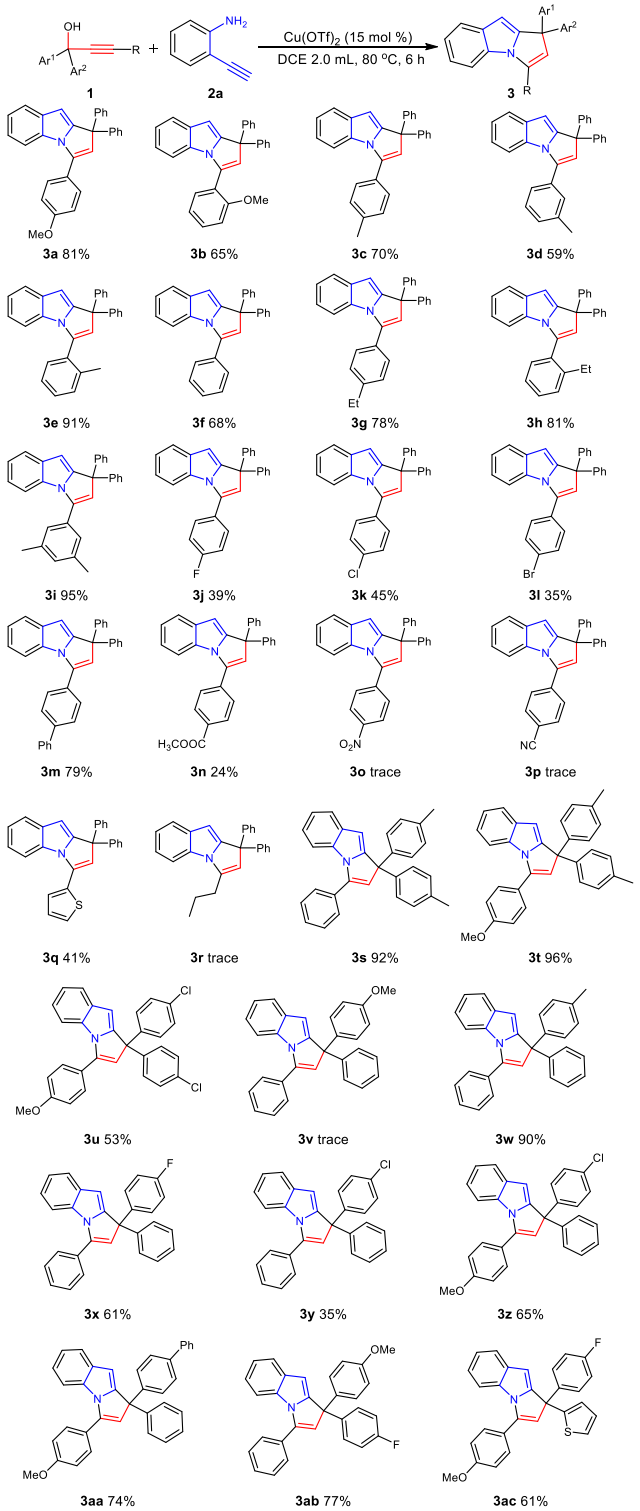
Scheme 2. Transformation of Propargylic Alcohols to 1*H*-pyrrolo[1,2-*a*]indoles [a, b]

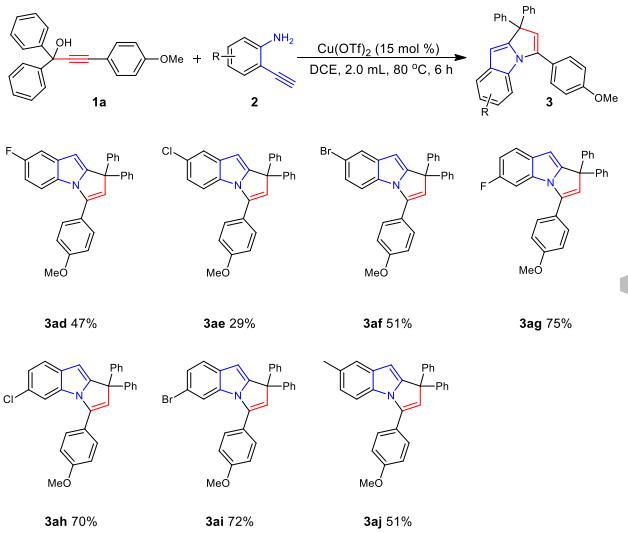


[a]Unless otherwise noted, all reactions were performed with **1** (0.1 mmol) and **2a** (2.0 equiv) in the presence of $Cu(OTf)_2$ (15 mol %) in DCE (2.0 mL) at 80 °C for 6 h. [b]Yields are given for isolated products.

furnishing the polycyclic products in moderate to good yields. Meanwhile, various substituent groups could be incorporated in different positions of the benzene ring (R), affording *ortho*-, *meta*-, and *para*-substituted 1*H*-pyrrolo[1,2-*a*]indole derivatives. Alkynol substrates containing substituents of varying electron-donating (OMe, Me, Et, and 3,5-diMe; **3a**–**3i**), electron-withdrawing character (Ph, COOMe; **3m**–**3n**), and halogen substituents (F, Cl, and Br; **3j**–**3l**), attached at any position of the aromatic ring (R), were compatible with this transformation and generated corresponding products **3a**–**3n** in yields ranging from 24% to 91%. Generally, substrates with electron-rich substituents were more favorable than those containing electron-deficient groups. In addition, halo-substituted 1*H*-pyrrolo[1,2-*a*]indole derivatives could be used as handles for further cross-coupling reactions. Thienyl-substituted propargylic alcohol **1q** was amenable to this transformation and gave the corresponding product **3q** in 41% yield. Symmetrical propargylic alcohols functionalized with electron-donating (Me, **3s**–**3t**) and electron-withdrawing substituents (Cl, **3u**) were all suitable substrates, generating the corresponding products in moderate to excellent yields. Furthermore, this transformation was applicable to a range of unsymmetrical alkynol substrates bearing electron-rich and electron-deficient substituents (**3w**–**3ac**). However, substrates containing electron-withdrawing moieties, such as nitro and cyano groups, as well as the alkyl substituent *n*-propyl, did not undergo the cascade annulation reaction under the standard conditions.

Subsequently, we conducted analogous batch reactions with respect to 2-ethynylanilines under the optimized conditions (Scheme 3). Various 2-ethynylaniline substrates **2ad**–**2aj**, bearing a range of halogen and alkyl groups on the aromatic ring moiety (R), were suitable for this cyclization reaction, delivering 1*H*-pyrrolo[1,2-*a*]indoles **3ad**–**3aj** in moderate to good yields. *4*-Substituted 2-ethynylaniline substrates bearing either electron-

Scheme 3. Transformation of Propargylic Alcohols to 1*H*-pyrrolo[1,2-*a*]indoles [a, b]



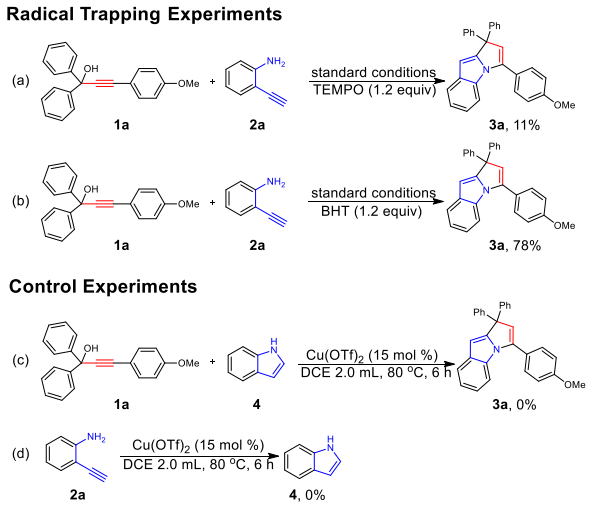
[a]Unless otherwise noted, all reactions were performed with **1** (0.1 mmol) and **2** (2.0 equiv) in the presence of $Cu(OTf)_2$ (15 mol %) in DCE (2.0 mL) at 80 °C for 6 h. [b]Yields are given for isolated products.

withdrawing or electron-donating groups, such as F, Cl, Br, and methyl on the aromatic ring (R) were found to be tolerated, giving the desired products (**3ad**−**3af, 3aj**) in 31−51% yields. The reactions of 5-substituted 2-ethynylanilines (**5ag**–**5ai**) with **1a** proceeded smoothly, furnishing moderate to good yields of the corresponding cascade annulation products. In general, 5-substituted 2-ethynylanilines reacted smoothly to deliver the corresponding products in good yields, displaying superior reactivity compared to the *4*-substituted 2-ethynylaniline substrates.

To further showcase the synthetic compatibility of our developed reaction system, a gram scale experiment was performed under the standard conditions for 14 h, and the corresponding cascade annulation product **3a** was isolated in 63% yield. The result portrays the potentials of this transformation in the synthetic industry.

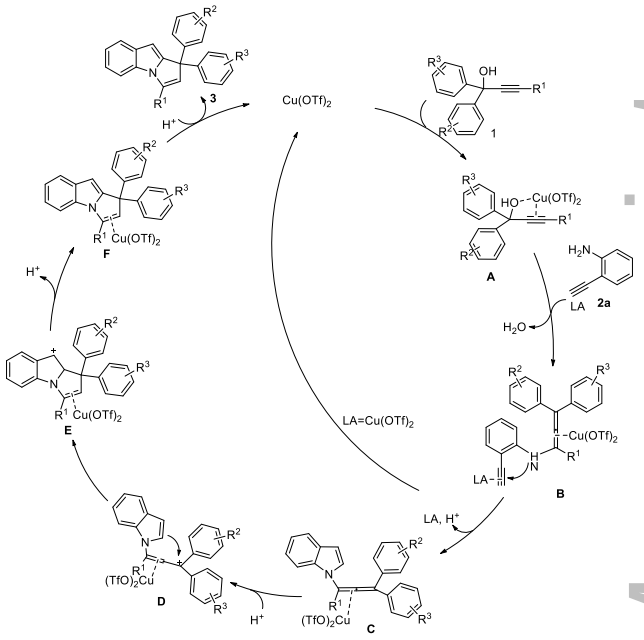
To explore the transformation process of the reaction, some necessary inhibition experiments were carried out, the radical scavengers 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) and 2,6-di-*tert*-butyl-4-methylphenol (BHT) were added into the reactions (Scheme 4a, b). The desired products were isolated in 11% and 78% yield, which excluded that a radical process might be involved. When propargylic alcohol **1a** was used as the substrate to react with 1*H*-indole **4** under the standard conditions, the expected product **3a** was not detected, and the reaction of 2-ethynylaniline (**2a**) could not give corresponding product 1*H*-indole **4** under the optimal conditions, indicating that 1*H*-indole **4** was not a intermediate of this transformation (Scheme 4c, d).

Scheme 4. Verification Experiments for the Mechanism



Based on the above results and previous literature[16-17], a tentative mechanism accounting for this cascade annulation is depicted in Scheme 5. The active propargyl intermediate **A**, which is formed in situ from propargylic alcohol **1** in the presence of a Lewis acid catalyst, would react with nucleophilic 2-ethynylaniline to yield intermediate **B**. The subsequent 5-endo-dig carbocyclization of intermediate **B** onto the terminal alkyne followed by the release of a proton produces the intermediate **C**, which could be further converted into intermediate **D** by protonation. Intramolecular nucleophilic attack of intermediate **D** to the carbocation site gives intermediate **E**, which could produce intermediate **F** by release of a proton. The desired product **3** is afforded *via* a proton exchange process with the regenerated catalyst.

Scheme 5. Proposed Mechanism for the Formation of 1*H*-pyrrolo[1,2-*a*]indoles



In summary, we have established a novel and efficient Lewis acid-catalyzed sequential intermolecular nucleophilic addition and 5-endo-dig carbocyclization of propargylic alcohols with 2-ethynylanilines, thereby to afford the synthetically valuable 1*H*-pyrrolo[1,2-*a*]indole derivatives in moderate to excellent yields under mild reaction conditions. This protocol offers versatile, environmentally benign, and atom-economical method of accessing the tricyclic structural motif, featuring good functional group compatibility, readily available starting materials, highly efficient catalytic system, operational simplicity.

Experimental Section

General Procedure for the Synthesis of Compounds 3

The reactions of propargylic alcohols **1** (0.1 mmol), and substituted 2-ethynylanilines **2** (2.0 equiv), $Cu(OTf)_2$ (15 mol %) in DCE (2.0 mL) were conducted at 80 °C under an air atmosphere for 6.0 h. The reactions were completed by TLC monitoring. The resulting mixtures were cooled down to room temperature. The mixtures were evaporated under reduced pressure. The residues were further purified by chromatography on silica gel **(**ethyl acetate/petroleum ether 1:100) to afford the corresponding products **3**.

Scale-Up Experiment

The reaction of propargylic alcohols **1a** (3.2 mmol), and 2-ethynylaniline **2a** (2.0 equiv), $Cu(OTf)_2$ (15 mol %) in DCE (10.0 mL) was conducted at 80 °C under an air atmosphere for 14.0 h. The reaction was completed by TLC monitoring. The resulting mixture was cooled down to room temperature. The mixture was evaporated under reduced pressure. The residue was further purified by chromatography on silica gel **(**ethyl acetate/petroleum ether 1:100) to afford the corresponding product **3a** in 63% yield (0.83 g).

Acknowledgements

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[15] CCDC 1959010 (**3c**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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UPDATE

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