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ARTICLE

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Lewis acid-activated ambiphilic reactivity on N-furan-2-ethynylanilines toward the synthesis of cyclopenta[*b*]indoles

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Abstract

A novel efficient method provides sustainable synthetic access to multi-substituted cyclopenta[*b*]indole derivatives is reported. Building upon established synthetic protocols, which often employ noble metal catalysts and demanding conditions, this strategy introduces a molecular designed N-furan aniline for cost-effective and environmentally conscious alternative. The strategy utilizes stoichiometric, readily available aluminum chloride ($AlCl_3$) under mild conditions, providing broad access to diverse cyclopenta[*b*]indole derivatives. The proposed mechanism shows that Lewis acid activation triggers a selective ring-opening of the furan, which is crucial for forming the cyclopenta[*b*]indole framework. The demonstrated synthetic utility, including the facile conversion of the scaffold into diazo and tosylhydrazone derivatives, underscores the potential of this methodology for constructing diverse, complex bioactive molecules, such as those related to Etrasimod and Fischerindole L.

KEYWORDS
annulation, aluminum chloride, cyclopenta[*b*]indole, Lewis acid

INTRODUCTION

Nitrogen-containing heterocyclic compounds represent a predominant structural motif found in natural products, pharmaceutical agents, agrochemicals, and a wide array of bioactive molecules.[1] Consequently, the development of efficient synthetic methods for constructing N-heterocycles remains a key objective in contemporary organic synthesis.[2,3] Among them, cyclopenta[*b*]indole derivatives represent a privileged structural motif in both natural and synthetic bioactive molecules. Their rigid polycyclic framework, which combines an indole core with a fused cyclopentane ring, endows these compounds with unique conformational and electronic properties. Such features often translate into high binding affinity and selectivity toward biological targets, making this scaffold a recurrent structure in natural products and pharmaceuticals.

Representative naturally occurring cyclopenta[*b*]indoles include Fischerindole L from cyanobacteria, Yuehchukene isolated from the *Murraya* genus, and Bruceloline J obtained from plants of the genus *Brucea*. These molecules exhibit remarkable biological activities such as cytotoxic, antifeedant, and antifertility effects. For instance, Fischerindole L shows cytotoxicity against lung cancer cell lines,[4,5] while Yuehchukene exhibits estrogenic activity,[6,7] the primary role of Bruceolines has been in the management of parasitic illnesses, such as malaria.[8,9] Furthermore, drugs such as Laropiprant, which features this scaffold, used in combination with nicotinic acid to reduce blood cholesterol.[10] In addition to their biological relevance, cyclopenta[*b*]indoles also find applications in materials science. For example, these frameworks can function as cyclopentadienyl-type ligands in metallocene complexes. Such metallocene catalysts are widely utilized in olefin polymerization (Figure 1).[11,12]

Due to the structural complexity and notable biological activities associated with cyclopenta[*b*]indole derivatives,

Alina Dzhaparova and You Jin Son contributed equally to this article.

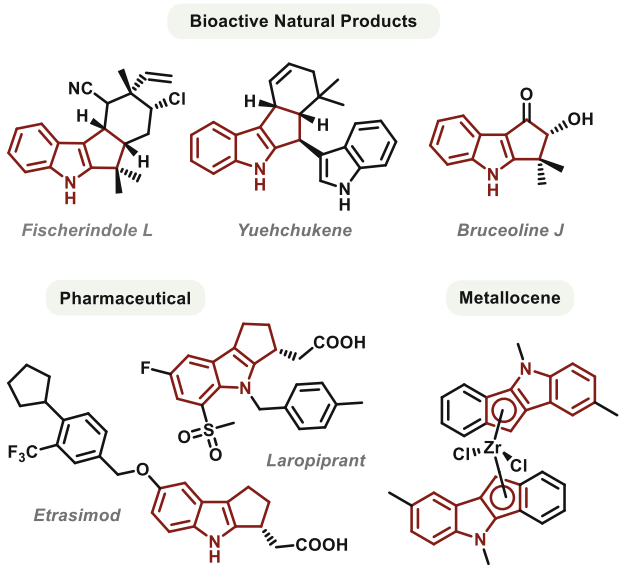


FIGURE 1 Selected examples of biologically active natural products and drugs containing cyclopenta[*b*]indoles.

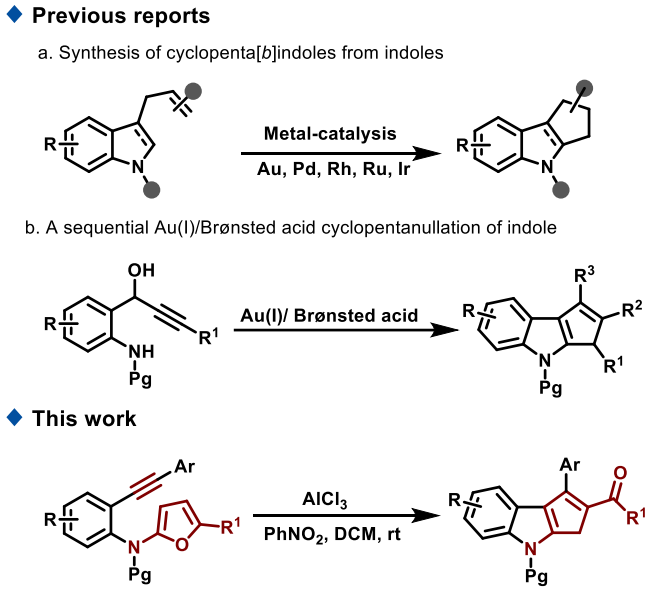


FIGURE 2 Precedents and our strategy for the synthesis of cyclopenta[*b*]indoles.

extensive efforts have been directed toward developing efficient synthetic strategies for accessing this privileged heterocyclic scaffold. Over the past decades, numerous methods have been introduced to build the cyclopenta[*b*]indole framework, reflecting the continual interest in harnessing its chemical diversity and therapeutic potential. A major driving force in this field has been the search for practical, operationally simple, and diversity-oriented protocols that can provide broad substrate compatibility while making use of readily accessible starting materials.

Among those approaches, metal-catalyzed transformations of indole derivatives have been widely explored as a means to construct the cyclopenta[*b*]indole framework. These reactions often proceed through cascade or annulation pathways that generate polycyclic structures.[13–17] In 2015, for example, the Ramasastry group reported a gold/Brønsted acid cooperative catalysis system that efficiently delivered multi-substituted cyclopenta[*b*]indoles in a single operation (Figure 2b).[18] This study demonstrated the strong potential of Au catalysis to orchestrate sequential activation events within indole frameworks. Later, in 2018, the same group employed a palladium-catalyzed intramolecular Trost–Oppolzer-type Alder–Ene reaction to access cyclopentadiene, one of which featured a disubstituted cyclopenta[*b*]indole.[19] Despite their synthetic utility, these methods share important limitations: both rely on noble metal catalysts such as gold and palladium, and each requires relatively harsh or tightly controlled reaction conditions.

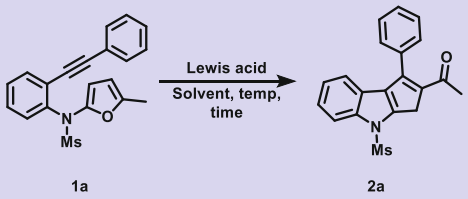
In this study, we introduce a mild and practical method for synthesizing previously unreported cyclopenta[*b*]indole derivatives using $AlCl_3$, an abundant, inexpensive, and non-noble Lewis acid (Figure 2, bottom). Motivated by the intrinsic high reactivity of amino-furan derivatives, we sought to develop an N-heteroarylation strategy that exploits their unique chemical behavior. We envisioned that the combination of N-furans and alkynes could unlock unconventional reactivity modes not accessible with traditional indole precursors.

Herein, we disclose a divergent reaction pathway in which amino-furan substrates undergo $AlCl_3$-mediated ring opening and exhibit previously unrecognized dual reactivity—acting both as an electrophile and a nucleophile within the same transformation. This unusual reactivity enables a sequential annulation process that forges two new rings, ultimately delivering cyclopenta[*b*]indoles with a fused polycyclic framework.

RESULTS AND DISCUSSION

A Lewis acid screening was carried out to evaluate the reactivity of substrate **1a** under various conditions for promoting furan ring opening followed by cyclization to the cyclopenta[*b*]indole framework. As summarized in Table 1, the direct addition of solid $AlCl_3$ to a DCM solution of **1a** resulted in only moderate efficiency (69% yield, Entry 1), likely due to incomplete dissolution of $AlCl_3$ in DCM and its rapid hydrolysis upon exposure to atmospheric moisture, which generated heterogeneous conditions and led to decomposition pathways. To address this issue, a homogeneous 1.0 M solution of $AlCl_3$ in nitrobenzene was employed, which delivered the desired product in significantly improved yield (93%, Entry 2) and established the optimized conditions for this transformation. Nitrobenzene, as a polar and coordinating solvent, dissolves $AlCl_3$ completely and ensures uniform activation throughout the reaction medium, which accounts for its superior performance over solid $AlCl_3$ in DCM. The use of

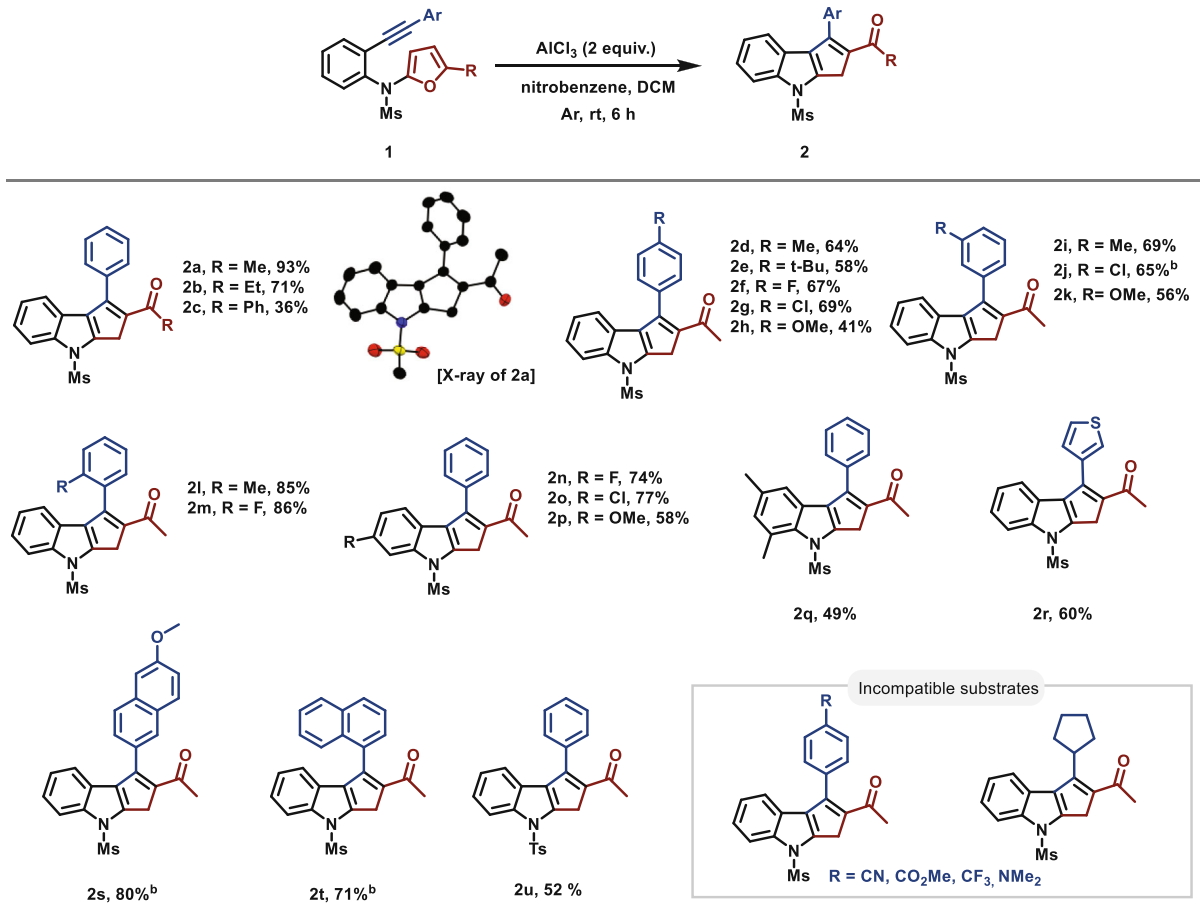
TABLE 1 Optimization of reaction conditions.



Entry	Lewis acid[a]	Equiv.	Solvent/temp	Time, h	Yield (%)[b]
1	$AlCl_3$	2	DCM/rt	6	69
2	**$AlCl_3$ 1 M in $PhNO_2$**	**2**	**DCM/rt**	**6**	**93**
3	$AlBr_3$	2	DCM/rt	4	41
4	$TiCl_4$	2	DCM/ −78°C to rt	16	66
5	$InCl_3$	2	DCM/rt	16	0
6	$Bi(OTf)_3$	2	DCM/rt	12	0
7	TFA	2	DCM/rt	12	—

Note: The bold text shows the optimized condition of the reaction.
Abbreviation: DCM= dichloromethane.
[a]Reaction conditions: 1a (0.05 mmol), Lewis Acid (2 equiv), DCM (0.1 M), under an argon atmosphere at room temperature; Yields were determined by HPLC using biphenyl as internal standard.
[b]Isolated yield.

TABLE 2 Substrate scope of cyclopenta[*b*]indole derivatives.



$AlBr_3$ also promoted cyclization but provided only moderate conversion (41%, Entry 3), while $TiCl_4$ generated the cyclized product in 66% yield despite requiring low-temperature addition (−78°C → rt, Entry 4). Other Lewis acids, including $InCl_3$ and $Bi(OTf)_3$, exhibited minimal or no reactivity (0% and trace yields, Entries 5 and 6, respectively), indicating their inefficiency in activating **1a**. In contrast, the Brønsted acid trifluoroacetic acid (TFA) did not induce any transformation, and the starting material was fully recovered (*Entry 7*), confirming that Lewis acidity—rather than Brønsted acidity—is essential for this cyclization. Interestingly, when stoichiometric quantities of indium and bismuth salts were examined, the expected cyclopenta[*b*]indole formation was not observed, further emphasizing the unique effectiveness of aluminum-based Lewis acids in this system (see Data S1 for the full optimization table).

Using the optimized conditions identified (Entry 2, Table 1), we next examined the substrate scope by systematically varying both the furan and alkyne components to evaluate the generality of the cyclization process (Table 2). When the furan ring was substituted with simple alkyl groups such as methyl or ethyl, the reaction proceeded smoothly to furnish the corresponding cyclopenta[*b*]indole products in excellent yields (**2a**, **2b**), indicating that alkyl substituents do not interfere with the Lewis acid–mediated ring-opening and subsequent cyclization sequence. The structure of obtained cyclopentaindole was confirmed by single-crystal X-ray diffraction analysis (see the Data S1 for details).[20] In contrast, the use of a phenyl-substituted furan led to the formation of multiple byproducts, giving only modest yield of **2c**; this reduced efficiency is likely due to competing electrophilic activation pathways involving the aromatic substituent under strongly Lewis acidic conditions. To avoid these undesired pathways, 5-methylfuran was selected as the preferred furan core for further scope exploration.

Variation of the alkyne component revealed clear electronic and steric trends. Para- and meta-substituted phenylacetylenes afforded moderate yields of cyclized products (**2d**–**2k**), suggesting that a range of substituents can be accommodated as long as they do not strongly perturb the electron density of the alkyne. Notably, ortho-substitution resulted in substantially improved yields (**2l**, **2m**), likely due to steric hindrance that restricts rotation around the aryl–alkyne bond and favors a conformation more conducive to intramolecular cyclization. In addition to tuning the alkyne component, we also investigated the impact of substituents placed directly on the indole ring. Substrates bearing halo, methoxy, or dimethyl groups underwent smooth cyclization to furnish the corresponding products (**2n**–**2q**). The reaction also tolerated a broad range of heteroaryl and extended aromatic alkynes, such as thiophenyl- and naphthyl-substituted derivatives, which afforded the corresponding products (**2r**–**2t**) in moderate to good yields. These findings indicate that heteroaryl groups do not significantly coordinate to or deactivate $AlCl_3$ in a way that disrupts the crucial furan ring-opening step. In contrast, substrates containing amine substituents did not undergo cyclization, likely because strong coordination of $AlCl_3$ to the nitrogen both attenuates the nucleophilicity of the alkyne and simultaneously deactivates the Lewis acidity of $AlCl_3$. Likewise, alkynes bearing strongly electron-withdrawing groups such as CN, CO_2Me, or CF_3 were completely unreactive under the optimized conditions. This lack of reactivity arises from the significantly reduced nucleophilicity of these alkynes, which prevents their effective engagement in the ring-forming step. Notably, formation of product **2t** resulted in two distinct atropisomers, as revealed by chiral HPLC analysis, indicating that sterically demanding arylacetylenes can induce restricted rotation and give rise to axial chirality (see Data S1 for full analytical data).

Based on our experimental observations, we propose that the annulation of amino-furans proceeds through the mechanism outlined in Figure 3. Coordination of $AlCl_3$ to the furan oxygen of **1** forms a Lewis acid–base complex, which triggers furan ring opening and generates the ambiphilic ketenimine intermediate **A**.[21] This intermediate then undergoes intramolecular cyclization to afford the indole species **B**. A subsequent intramolecular cyclization produces intermediate **C**, which upon tautomerization and workup yields the fused cyclopentadiene–indole framework **2**. Notably 3-methyl furan, **1w** remained unreactive under the standard condition, presumably

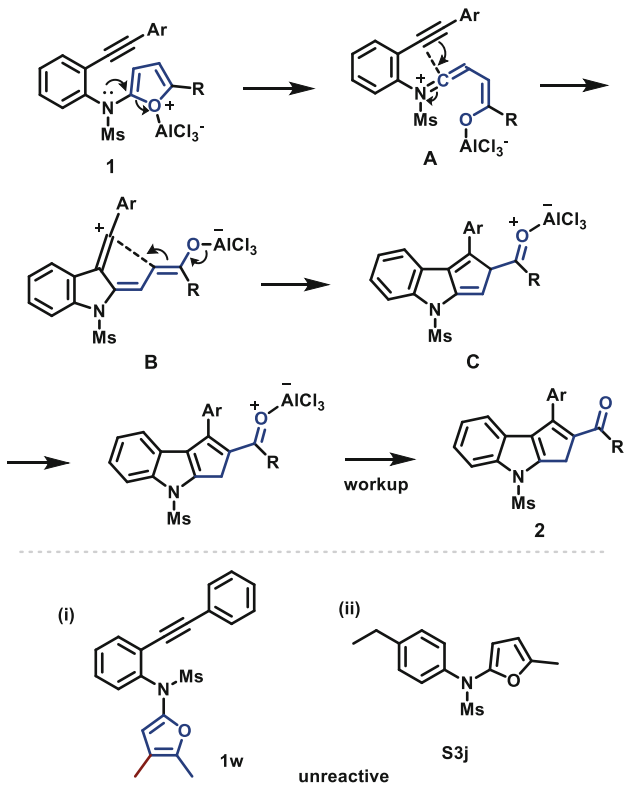


FIGURE 3 Proposed Mechanism for the Formation of Cyclopenta[*b*]indole.

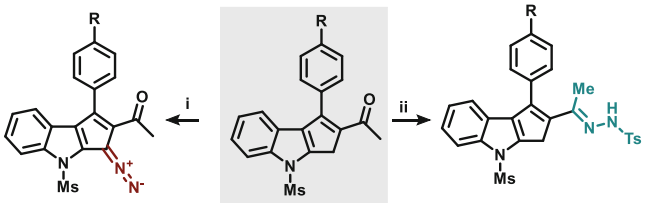


FIGURE 4 Post-synthetic Functionalization of Cyclopenta[*b*]indole.

dued to the steric congestion, and control experiment examining a possible intermolecular pathway confirmed that such a process is not operative.

The synthetic versatility of the cyclopenta[*b*]indole scaffold was demonstrated through post-synthetic functionalization. The methylene (CH_2) carbon of the cyclopentadiene ring was successfully transformed into a diazo compound **3a**, which are holds potential for applications involving carbene transfer reactions (Figure 4).

Furthermore, the ketone moiety was successfully transformed into an N, N-tosylhydrazone derivative **3b**, opening access to late-stage modifications. These modifications highlight the flexibility of the cyclopenta[*b*]indole framework and its potential as a platform for diverse synthetic applications.

CONCLUSION

In conclusion, we have demonstrated that *N*-furan-2-ethynylanilines undergo an efficient Lewis acid-activated cascade cyclization when treated with $AlCl_3$. The strong Lewis acidity of $AlCl_3$ promotes ring opening of the 2-aminofuran moiety, generating a highly reactive ambiphilic intermediate that drives the sequential cyclizations necessary to construct the fused cyclopenta[*b*]indole scaffold. This strategy provides a mild, cost-effective, and operationally simple method for accessing multi-substituted cyclopenta[*b*]indole derivatives in good to excellent yields. Furthermore, investigation of the substrate scope reveals clear electronic constraints: electron-rich alkynes are required for productive cyclization, whereas electron-deficient substrates fail to participate. These findings highlight a powerful alternative to noble-metal-catalyzed approaches for constructing this synthetically and biologically significant heterocyclic framework.

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DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supplementary material of this article.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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