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Organocatalytic Nazarov-type cyclization of 3-alkynyl-2-indolylmethanols: construction of axially chiral cyclopenta[*b*]indole scaffolds

Ping Wu[1,2], Xin-Yu Yan[2], Song Jiang[2], Yi-Nan Lu[2], Wei Tan[2,*], Feng Shi[1,2,*]

[1]School of Petrochemical Engineering, Changzhou University, Changzhou 213164, Jiangsu, China.
[2]School of Chemistry and Materials Science, Jiangsu Normal University, Xuzhou 221116, Jiangsu, China.

[*]**Correspondence to:** Prof. Wei Tan, School of Chemistry and Materials Science, Jiangsu Normal University, Shanghai Road No. 101, Xuzhou 221116, Jiangsu, China. E-mail: wtan@jsnu.edu.cn; Prof. Feng Shi, School of Petrochemical Engineering, Changzhou University, Gehu Road No. 21, Changzhou 213164, Jiangsu, China. E-mail: fshi@jsnu.edu.cn; fshi@cczu.edu.cn

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Abstract

In recent years, it has become an urgent task to design new types of indole-based platform molecules for Nazarov-type cyclizations and develop organocatalytic Nazarov-type cyclizations for synthesizing indole derivatives. To fulfill this task, in this work, by changing the alkynyl terminal substituent from *t*-Bu to an aryl group, the reactivity of 3-alkynyl-2-indolylmethanols is modulated and the new platform molecules serve as competent substrates for Brønsted acid-catalyzed Nazarov-type cyclization. Based on this new reactivity, the first organocatalytic Nazarov-type cyclization of aryl-substituted 3-alkynyl-2-indolylmethanols with 2-naphthols is accomplished, leading to the efficient construction of a new class of axially chiral 3, 4-dihydrocyclopenta[*b*]indole scaffolds. This preliminary investigation of organocatalytic asymmetric Nazarov-type cyclization provides an optional strategy for the atroposelective construction of this new class of axially chiral cyclopenta[*b*]indole scaffolds. In addition, the first preparation of axially chiral 3, 4-dihydrocyclopenta[*b*]indole with optical purity is established through chiral resolution, which could serve as a complementary method to catalytic asymmetric approaches.

Keywords: 2-indolylmethanol, Nazarov cyclization, organocatalysis, asymmetric organocatalysis, axial chirality

INTRODUCTION

Indoles belong to an important nitrogen-containing heterocyclic motif that is present in many bioactive natural products and pharmaceuticals[1-4]. Therefore, the construction of indole-based frameworks, particularly via organocatalysis, has become an important field of study[5-8]. Among indole-fused rings, cyclopenta[*b*]indoles are attractive frameworks[9-13], which constitute the core structures of many natural products and biologically important compounds, such as yuehchukene[9], bruceolline I[10], fischerindole L[11], thomitrem A[12] and MK-0524[13] [Figure 1].

As a result, the construction of such indole-containing scaffolds has remained a long-standing goal in the chemistry community[14-20] and many synthetic approaches have been developed for the synthesis of these important structural units[21-29]. Among these approaches, the Nazarov-type cyclization[30-37] for the construction of 1, 2, 3, 4-tetrahydrocyclopenta[*b*]indole scaffolds is undoubtedly one of the most step-economical and efficient methods[38-47]. However, the classical synthesis of such indole derivatives via Nazarov-type cyclizations has largely focused on the Lewis acid (LA)-catalyzed 4π-electrocyclizations of indole-fused 1,4-dien-3-ones, which involve the process of generating a pentadienyl cation **(I)** intermediate to form the corresponding 1, 2, 3, 4-tetrahydrocyclopenta[*b*]indoles [Scheme 1A][37-41]. Nevertheless, other Nazarov-type cyclizations for the construction of such scaffolds are rather rare[42-47]. In our previous work, we designed 3-alkenyl-2-indolylmethanols as a new class of indole-based platform molecules for Brønsted acid-catalyzed interrupted Nazarov-type cyclizations with various nucleophiles[45-47] based on the formation of a pentadienyl cation **(II)** intermediate to construct 1, 2, 3, 4-tetrahydrocyclopenta[*b*]indole scaffolds [Scheme 1B]. In spite of these approaches, there are still some challenges in this research field. The first is that the indole-derived substrates suitable for Nazarov-type cyclizations are confined to indole-fused 1, 4-dien-3-ones and 3-alkenyl-2-indolylmethanols. The second is that many Nazarov-type cyclizations are enabled by Lewis acid catalysis and organocatalytic Nazarov-type cyclizations are underdeveloped[40,48-56], even though organocatalysis has been proven to have tremendous advantages[57-63]. Therefore, it has become an urgent task to design new types of indole-based platform molecules for Nazarov-type cyclizations and develop organocatalytic Nazarov-type cyclizations for synthesizing indole derivatives.

To overcome these challenges and fulfill this task, based on our long-lasting interests in synthesizing indole derivatives via designing indole-based platform molecules and their involved organocatalytic reactions[5-8], we decided to design a new type of indole-based platform molecules for organocatalytic Nazarov-type cyclizations. In our previous work, we designed *t*-Bu-substituted 3-alkynyl-2-indolylmethanols for constructing axially chiral alkene-indole scaffolds via addition reactions [Scheme 2A]. Specifically, in the presence of a chiral Brønsted acid, this class of 3-alkynyl-2-indolylmethanols transformed into allene-iminium intermediates, which were readily attacked by nucleophiles to undergo 1, 4-addition, thus giving axially chiral alkene-indoles. When using dinucleophiles, the OH group of 2-indolylmethanols undergoes dehydration to give carbocation intermediates[64-72], which subsequently undergo an intramolecular addition reaction to generate axially chiral cyclic alkene-indoles[73,74]. In these previous studies, the *t*-Bu group, as an aliphatic and bulky group, was detrimental to the delocalization of carbocation, thus making this class of 3-alkynyl-2-indolylmethanols unsuitable for Nazarov-type cyclizations. On this basis, we considered changing the *t*-Bu group to a less steric aryl (Ar) group, thus making aryl-substituted 3-alkynyl-2-indolylmethanols suitable for Nazarov-type cyclizations [Scheme 2B]. This design is based on the consideration that the carbocation can readily undergo 4π electron delocalization due to the existence of the terminal aryl group, therefore undergoing Nazarov-type cyclization and constructing 3, 4-dihydro-cyclopenta[*b*]indoles.

Based on this concept, we design an organocatalytic Nazarov-type cyclization of aryl-substituted 3-alkynyl-2-indolylmethanols with 2-naphthols [Scheme 2C]. The selection of 2-naphthols as suitable nucleophiles is

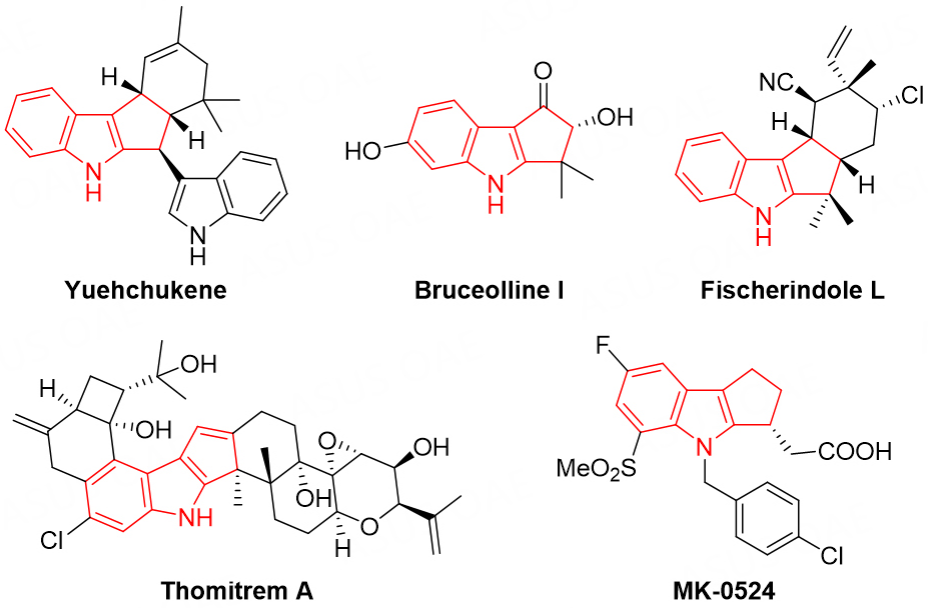


Figure 1. Representative natural products and bioactive compounds containing the cyclopenta[*b*]indole scaffold.

based on the consideration that 2-naphthols[75-77] are easily activated by Brønsted acids through the interaction of hydrogen bonding. It is noteworthy that 2-naphthols with a planar structure and the effect of steric congestion should lead to the formation of a C-C bond as a chiral axis[78-80], thus endowing the constructed cyclopenta[*b*]indole frameworks with axial chirality[81-89]. Therefore, the significance of this work is threefold: (1) modulating the terminal substituents of 3-alkynyl-2-indolylmethanols to achieve different reactivities; (2) the first organocatalytic Nazarov-type cyclization of aryl-substituted 3-alkynyl-2-indolylmethanols; (3) the efficient construction of a new class of axially chiral 3, 4-dihydrocyclopenta[*b*]indole scaffolds.

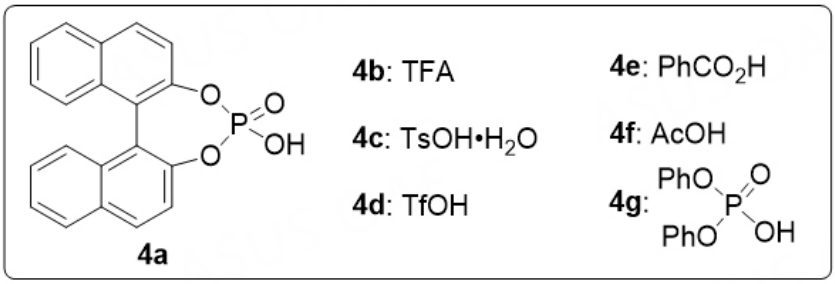
EXPERIMENTAL

To a mixture of 3-phenyl-2-indolylmethanol **1** (0.30 mmol), 2-naphthol **2** (0.2 mmol) and catalyst **4a** (7.0 mg, 0.02 mmol) was added $CHCl_3$ (1 mL). The reaction mixture was then stirred at 30 °C for 12 h. After the completion of the reaction, which was indicated by thin layer chromatography, the reaction mixture was directly purified through column chromatography on silica gel (petroleum ether:dichloromethane = 2:1 as eluent) to afford pure product **3**.

RESULTS AND DISCUSSION

Based on this design, we initially attempted the reaction of 3-alkynyl-2-indolylmethanol **1a** bearing a terminal phenyl group with 2-naphthol **2a** in the presence of 10 mol% racemic phosphoric acid **4a** in chloroform ($CHCl_3$) at 20 °C for 12 h [Table 1 and entry 1]. Gratifyingly, the designed Nazarov-type cyclization occurred in a facile manner to afford cyclopenta[*b*]indole **3aa** in a moderate yield of 55%. A series of Brønsted acids **4** were then evaluated for the reaction (entries 2-7), which revealed that *p*-toluenesulfonic acid monohydrate **4c** ($TsOH{\cdot}H_2O$) and trifluoromethanesulfonic acid **4d** (TfOH) could catalyze the reaction to some extent (entries 3 and 4), whereas other Brønsted acids could barely catalyze the reaction and only trace amounts of product were observed (entries 2 and 5-7). Therefore, racemic phosphoric acid **4a** was selected as the optimal catalyst for this Nazarov-type cyclization. Subsequently, several different types of solvents were screened (entries 8-12). It was found that the reaction could only

Table 1. Screening of catalysts and optimization of reaction conditions[a]

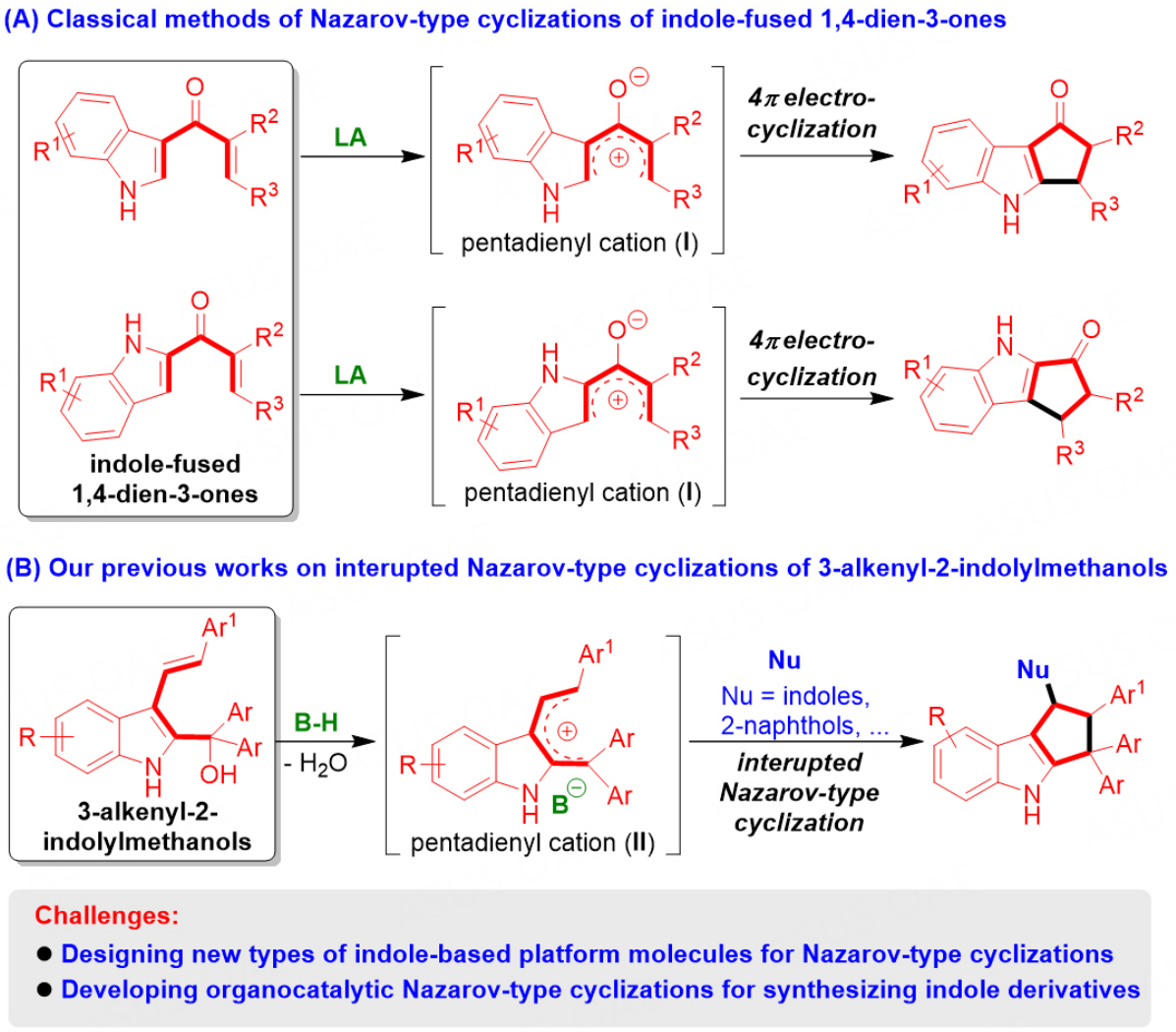


1a 2a 3aa

Entry	Cat.	Solvent	T (°C)	1a: 2a	Yield (%)[b]
1	**4a**	$CHCl_3$	20	1:1.2	55
2	**4b**	$CHCl_3$	20	1:1.2	trace
3	**4c**	$CHCl_3$	20	1:1.2	45
4	**4d**	$CHCl_3$	20	1:1.2	11
5	**4e**	$CHCl_3$	20	1:1.2	trace
6	**4f**	$CHCl_3$	20	1:1.2	trace
7	**4g**	$CHCl_3$	20	1:1.2	trace
8	**4a**	toluene	20	1:1.2	43
9	**4a**	acetone	20	1:1.2	trace
10	**4a**	MeCN	20	1:1.2	trace
11	**4a**	THF	20	1:1.2	trace
12	**4a**	EtOAc	20	1:1.2	trace
13	**4a**	$CHCl_3$	20	1:1.5	64
14	**4a**	$CHCl_3$	20	1.2:1	62
15	**4a**	$CHCl_3$	20	1.5:1	70
16[c]	**4a**	$CHCl_3$	20	1.5:1	76
17[d]	**4a**	$CHCl_3$	20	1.5:1	61
18[e]	**4a**	$CHCl_3$	20	1.5:1	37
19[c]	**4a**	$CHCl_3$	30	1.5:1	85
20[c]	**4a**	$CHCl_3$	40	1.5:1	79

[a]Unless otherwise indicated, the reaction was carried out at a 0.1 mmol scale and catalyzed by 10 mol% **Cat.** in a solvent (1.0 mL) at the indicated temperature for 12 h; [b]Isolated yield; [c]Performed in 0.5 mL of $CHCl_3$; [d]Performed in 2.0 mL of $CHCl_3$; [e]Performed in 3.0 mL of $CHCl_3$.

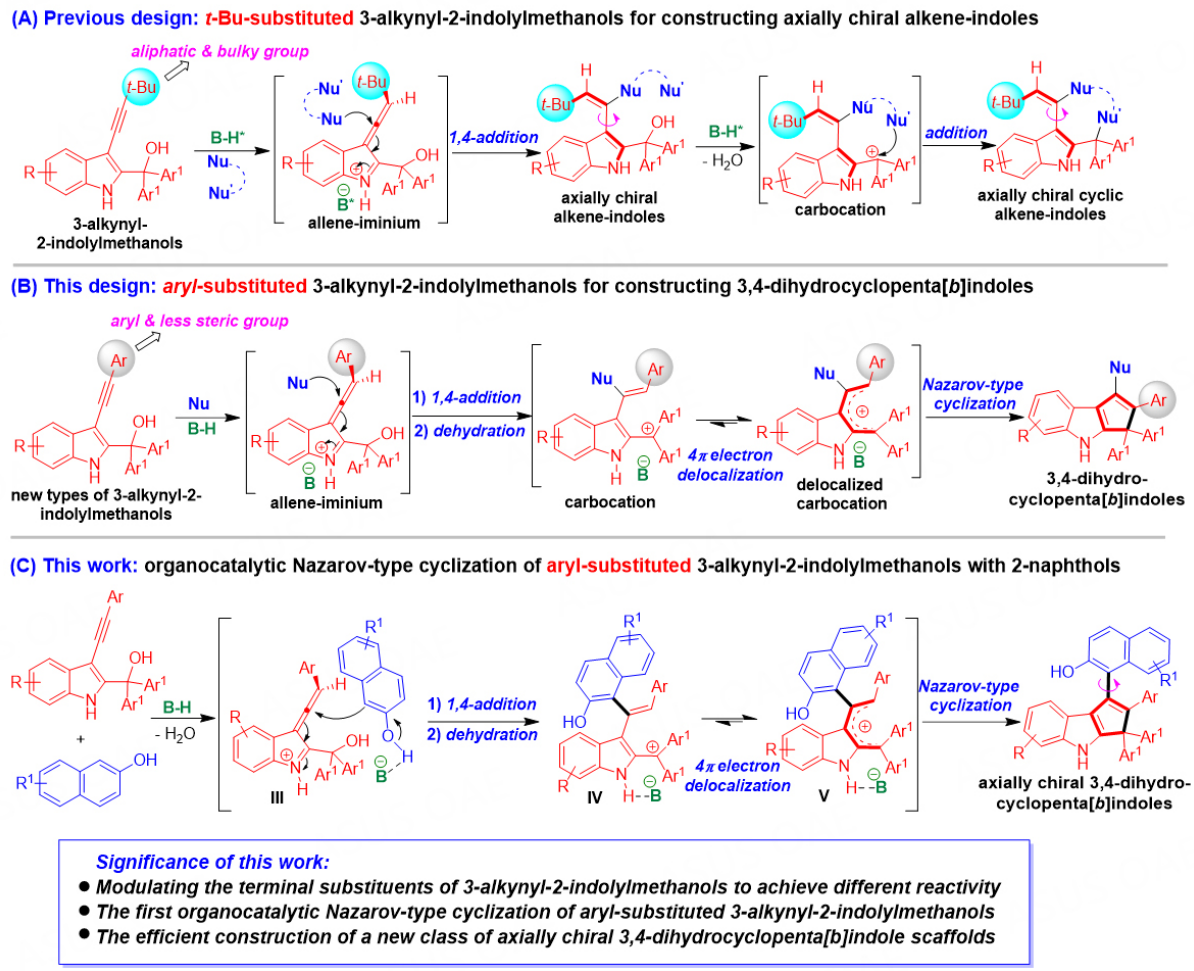
occur in chloroform (entry 1) and toluene (entry 8), with chloroform acting as a better reaction medium in terms of yield. To further improve the yield of this model reaction, other reaction parameters, such as reagent ratio and reaction concentration and temperature, were modulated (entries 13-20). It was found



Scheme 1. Profile of the construction of 1, 2, 3, 4-tetrahydrocyclopenta[*b*]indole scaffolds via Nazarov-type cyclizations.

that the yield of product **3aa** could be improved by modulating the ratio of **1a** and **2a** (entries 13-15). When the ratio was adjusted to 1.5:1, the yield of product **3aa** could be increased to 70% (entry 15). In addition, the subsequent evaluation of the reaction concentration (entries 16-18) revealed that a higher concentration was helpful for increasing the yield (entry 16), i.e., when the reaction was performed in 0.5 mL $CHCl_3$, product **3aa** could be obtained in a higher yield of 76% (entry 16). Finally, slightly modulating the reaction temperature (entries 19 and 20) resulted in the yield of product **3aa** being further improved to 85% when performing the reaction at 30 °C (entry 19). Therefore, the optimal conditions for the Nazarov-type cyclization were set as those of entry 19.

With the optimal reaction conditions determined, we then investigated the substrate scope of the Nazarov-type cyclization [Figure 2]. First, the substrate scope of the 3-alkynyl-2-indolylmethanols **1** was studied by reactions with indole **2a**. As shown in Figure 2, the Brønsted acid-catalyzed Nazarov-type cyclization was compatible with a variety of substrates **1** bearing different R/Ar/Ar^1 substituents, which successfully participated in the reaction to give the expected 3, 4-dihydrocyclopenta[*b*]indoles **3** in moderate to good yields. Specifically, the terminal Ar substituents of the alkyne functionality in the structures of 3-alkynyl-2-



Scheme 2. Design of a new type of 3-alkynyl-2-indolylmethanols for constructing 3, 4-dihydrocyclopenta[*b*]indoles via organocatalytic Nazarov-type cyclization.

indolylmethanols **1** could be *para*- and *meta*-substituted phenyl groups with different electronic natures and these substrates successfully engaged in the reaction to deliver the corresponding products **3ba-3ga** in generally high yields. In addition, the R substituents on the indole ring could be changed and C5- and C6-substituted substrates **1h-1j** were employed in the reaction for synthesizing 3, 4-dihydrocyclopenta[*b*] indoles **3ha-3ja** in moderate yields. Regarding the Ar^1 substituents, *meta*- and *para*-substituted phenyl groups with either electron-donating or electron-withdrawing properties proved to be suitable substituents for substrates **1k-1n**, which readily took part in the Nazarov-type cyclization to give the desired 3, 4-dihydrocyclopenta[*b*]indole products **3ka-3na** in moderate to good yields (57%-71%).

Next, the substrate scope of 2-naphthols **2** was investigated by the Nazarov-type cyclization with 3-alkynyl-2-indolylmethanol **1a**. As shown in Figure 2, this reaction was amenable to a series of C6- and C7-substituted 2-naphthols **2b-2i**, which underwent the Nazarov-type cyclization to afford the desired products **3ab-3ai** in moderate to good yields. In detail, C6-substituted 2-naphthols **2**, regardless of their electronic nature, could be applicable to the reaction, and it was found that 2-naphthol **2c** with an electron-donating group could give product **3ac** in the highest yield of 86%. For C7-substituted 2-naphthols **2**, various substituents with electron-donating or electron-withdrawing properties were tolerant to the reaction and 2-

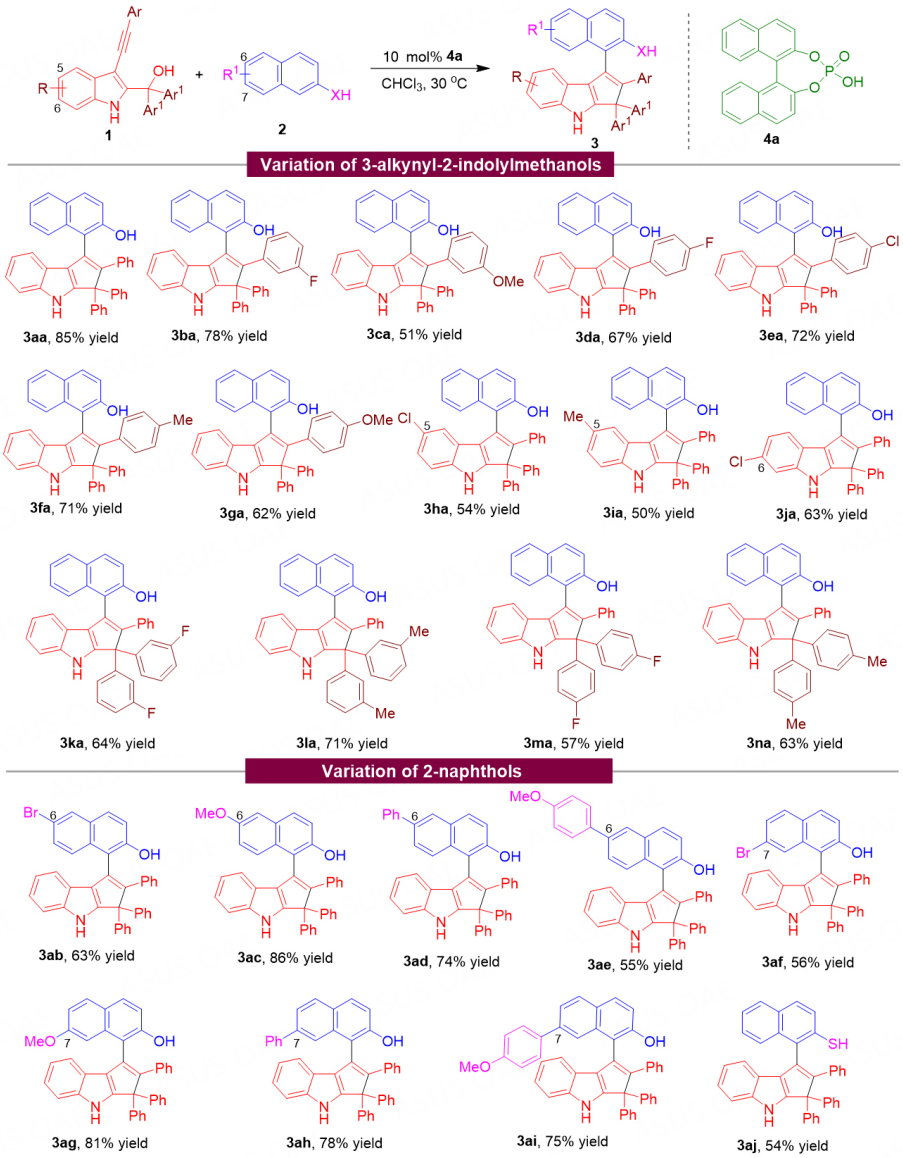
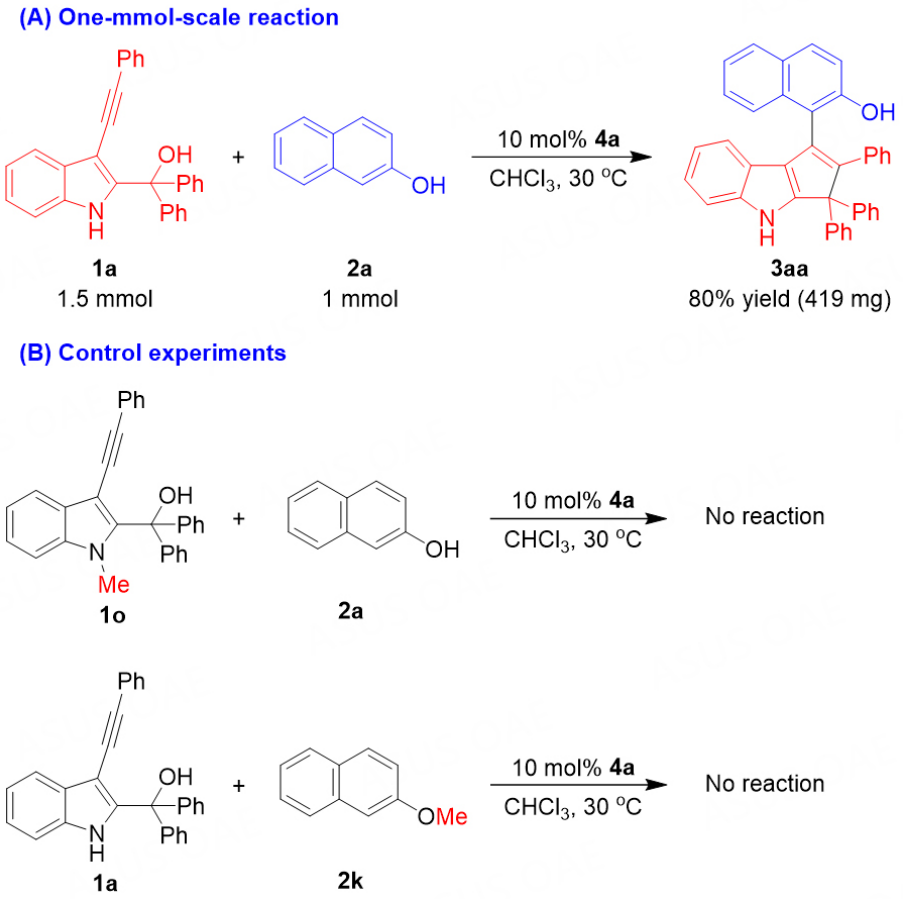


Figure 2. Substrate scope of Nazarov-type cyclization. Reaction conditions: 0.2 mmol scale; 10 mol% **4a**; $CHCl_3$ (1.0 mL); 30 ℃; 12 h; **1**: **2** = 1.5:1. Isolated yields.

naphthol **2g** with a C7-methoxyl group could furnish product **3ag** in a high yield of 81%. Interestingly, 2-naphthalenethiol **2j** serving as an analogue of 2-naphthol **2a** could be employed for the Nazarov-type cyclization under the standard conditions, giving product **3aj** in a moderate yield.

In addition, we performed a 1 mmol scale reaction of 3-alkynyl-2-indolylmethanol **1a** with 2-naphthol **2a** under the optimal reaction conditions [Scheme 3A]. In this case, product **3aa** was afforded in a high yield of 80%, which demonstrated that this Brønsted acid-catalyzed Nazarov-type cyclization could be scaled up and should have potential applications. In order to gain some insights into the organocatalytic Nazarov-type cyclization, we performed some control experiments [Scheme 3B]. First, *N*-methyl-protected 3-alkynyl-2-indolylmethanol **1o** was employed as a substrate to the reaction with 2-naphthol **2a** under the standard reaction conditions with no reaction observed, which indicated that the NH group of 3-alkynyl-2-indolylmethanol **1** played an important role in controlling the reactivity. Second, *O*-methyl-protected

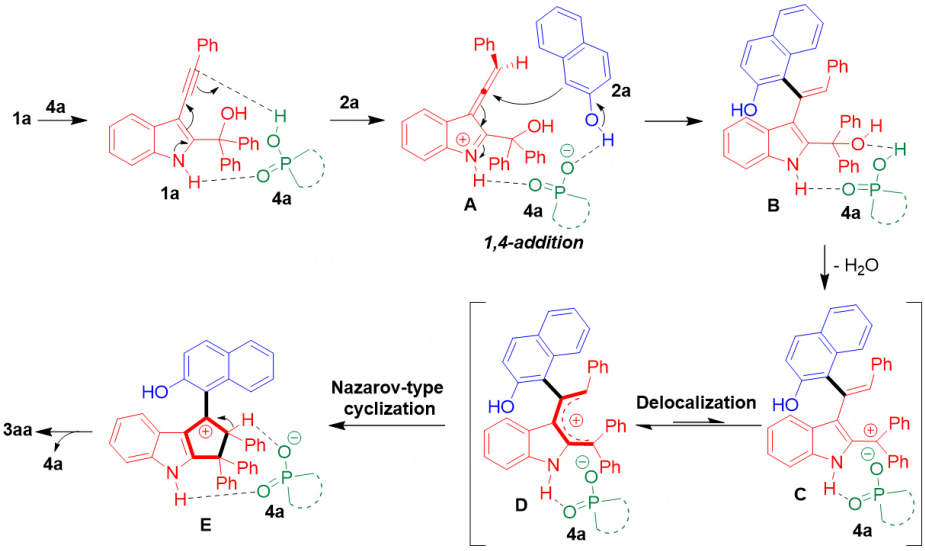


Scheme 3. One mmol scale reaction and control experiments.

substrate **2k** was used as a nucleophile to react with **1a** and still no reaction occurred. This result demonstrated that the OH group of substrate **2** was necessary for performing the reaction.

Based on the control experiments, a possible reaction pathway and activation mode of this Brønsted acid-catalyzed reaction were proposed [Scheme 4]. As exemplified by the model reaction, 3-alkynyl-2-indolylmethanol **1a** was initially transformed into allene-iminium intermediate **A** under the activation of Brønsted acid **4a** via hydrogen-bonding interaction. Subsequently, catalyst **4a** simultaneously activated allene-iminium intermediate **A** and 2-naphthol **2a** via forming two hydrogen bonds, thus facilitating a 1, 4-addition between them to generate intermediate **B**. Intermediate **B** then experienced a dehydration process under the catalysis of Brønsted acid **4a** to give carbocation **C**, which was easily converted into 4π carbocation **D** due to electron delocalization. Finally, activated by catalyst **4a** via the interactions of hydrogen bonding and ion pairing, intermediate **D** underwent a Nazarov-type cyclization to form the cyclic carbocation intermediate **E**, which immediately underwent α-H elimination to deliver 3, 4-dihydrocyclopenta[*b*]indole **3aa** with the regeneration of catalyst **4a**.

Because this class of 3, 4-dihydrocyclopenta[*b*]indole scaffolds **3** contains a carbon-carbon chiral axis, we then carried out a preliminary investigation on the organocatalytic asymmetric version of the Nazarov-type cyclization. In fact, in recent years, the catalytic asymmetric construction of axially chiral indole-based scaffolds has become an emerging area of study[8,78] due to the importance of such scaffolds in many natural

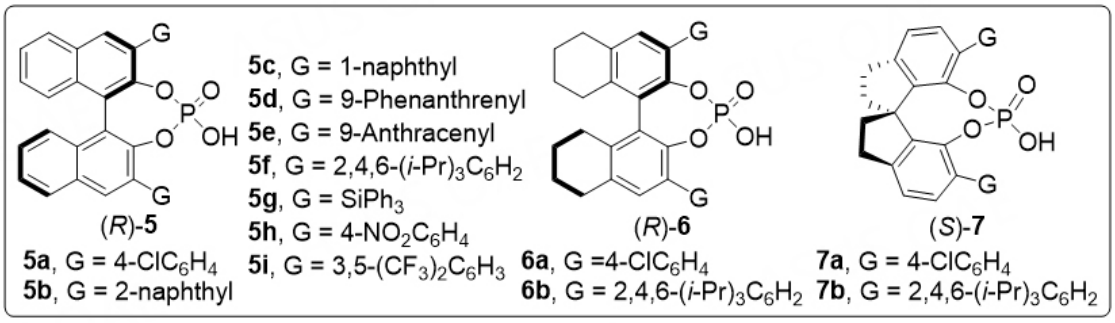


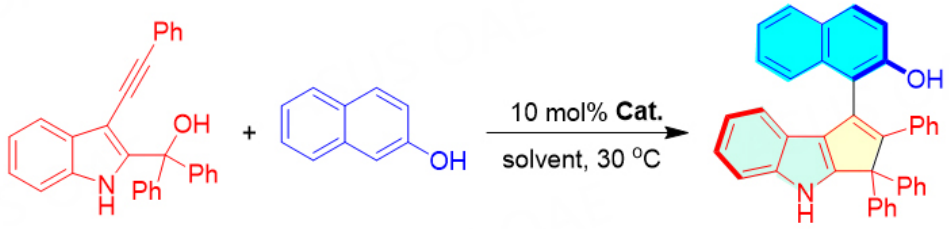
Scheme 4. Suggested reaction pathway.

products[90-92], bioactive molecules[93,94] and chiral catalysts or ligands[95-101]. Although a number of axially chiral indole-based scaffolds, such as *N*-arylindoles[102-110], 3-arylindoles[111-120], 2-arylindoles[121-127], 3-quinonylindoles[128,129], isochromenone-indoles[130], bisindoles[131-135] and other indole derivatives[136-143], have been successfully synthesized, the catalytic asymmetric construction of axially chiral 3, 4-dihydrocyclopenta[*b*]indole scaffolds is unknown. As shown in Table 2, a series of chiral phosphoric acids (CPAs)[144-151] **5-7** were chosen as chiral organocatalysts to promote the reaction between **1a** and **2a** (entries 1-13). As expected, axially chiral cyclopenta[*b*]indole **3aa** could be obtained in an atroposelective manner. Particularly, when CPA (*S*)-**5f** was used as a chiral organocatalyst, axially chiral product **3aa** was generated with an atroposelectivity of 47% ee, albeit with an extremely low yield of 7% (entry 6). Under the catalysis of CPA (*S*)-**5f**, several different types of solvents were examined (entries 14-18), which disclosed that only toluene could serve as an effective reaction media to deliver axially chiral product **3aa** in 69% ee and 11% yield (entry 14). Subsequently, to further improve the atroposelectivity and the yield of product **3aa**, we attempted to modulate the catalyst loading in the reaction (entries 19 and 20). When the catalyst loading of (*S*)-**5f** was increased to 20 mol%, product **3aa** was generated in a slightly improved yield of 20% with the retained atroposelectivity of 69% ee (entry 20). These preliminary results implied that simultaneously controlling both the enantioselectivity and the yield of this organocatalytic asymmetric Nazarov-type cyclization is a significant challenge. Although the yield and atroposelectivity of axially chiral product **3aa** in this organocatalytic asymmetric version are not satisfactory, this organocatalytic asymmetric Nazarov-type cyclization provides an optional strategy for the atroposelective construction of this new class of axially chiral cyclopenta[*b*]indole scaffolds.

Finally, to obtain the two enantiomers of axially chiral **3aa**, we tried using the strategy of chiral resolution [Scheme 5]. In detail, the racemic compound *rac*-**3aa** was subjected to the acylation reaction with (*R*)-(-)-*O*-formylmandeloyl chloride (*R*)-**8** as a resolution reagent in the presence of DMAP, which gave rise to two separable diastereomers (S_a, *R*)-**9** and (R_a, *R*)-**9**. By treating with hydrazine hydrate, the two diastereomers were then easily transformed into the corresponding single enantiomers (S_a)-**3aa** and (R_a)-**3aa**, respectively, in high yields with excellent atroposelectivities. In this manner, the first preparation of axially chiral 3, 4-dihydrocyclopenta[*b*]indoles with optical purity was established, which could serve as a complementary method to catalytic asymmetric approaches. Moreover, the absolute configuration of product (S_a)-**3aa** was

Table 2. Preliminary investigation of organocatalytic asymmetric version of Nazarov-type cyclization[a]



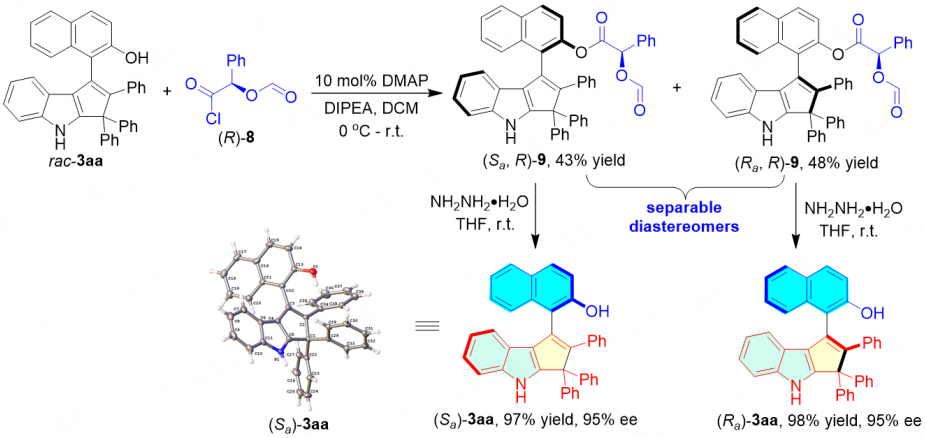


1a **2a** (S_a)-**3aa**

Entry	Cat.	Solvent	Yield (%)[b]	ee (%)[c]
1	**5a**	$CHCl_3$	85	12
2	**5b**	$CHCl_3$	32	10
3	**5c**	$CHCl_3$	trace	-
4	**5d**	$CHCl_3$	21	27
5	**5e**	$CHCl_3$	10	4
6	**5f**	$CHCl_3$	7	47
7	**5g**	$CHCl_3$	trace	-
8	**5h**	$CHCl_3$	89	2
9	**5i**	$CHCl_3$	47	10
10	**6a**	$CHCl_3$	58	15
11	**6b**	$CHCl_3$	trace	-
12	**7a**	$CHCl_3$	34	16
13	**7b**	$CHCl_3$	trace	-
14	**5f**	toluene	11	69
15	**5f**	EtOAc	trace	-
16	**5f**	THF	trace	-
17	**5f**	MeCN	trace	-
18	**5f**	acetone	trace	-
19[d]	**5f**	toluene	9	68
20[e]	**5f**	toluene	20	69

[a]Unless otherwise indicated, the reaction was carried out at a 0.1 mmol scale and catalyzed by 10 mol% **Cat.** in a solvent (1.0 mL) at 30 °C for 18 h and the molar ratio of **1a**:**2a** was 1.2:1; [b]Isolated yield; [c]Enantiomeric excess (*ee*) was determined by high-performance liquid chromatography; [d] Catalyzed by 5 mol% **5f**; [e]Catalyzed by 20 mol% **5f**.

determined by X-ray diffraction analysis[152] of its single crystal (see Supplementary Materials), which was obtained by recrystallization.



Scheme 5. Preparation of (*Sa*)-**3aa** and (*Ra*)-**3aa** by the strategy of chiral resolution.

CONCLUSION

In summary, by changing the alkynyl terminal substituent from *t*-Bu to an aryl group, the reactivity of 3-alkynyl-2-indolylmethanols was modulated as competent platform molecules for Brønsted acid-catalyzed Nazarov-type cyclization. Based on this new reactivity, we accomplished the first organocatalytic Nazarov-type cyclization of aryl-substituted 3-alkynyl-2-indolylmethanols with 2-naphthols, thus realizing the efficient construction of a new class of axially chiral 3, 4-dihydrocyclopenta[*b*]indole scaffolds. The preliminary investigation on the organocatalytic asymmetric Nazarov-type cyclization provided an optional strategy for atroposelective construction of this new class of axially chiral cyclopenta[*b*]indole scaffolds. In addition, we realized the first preparation of axially chiral 3, 4-dihydrocyclopenta[*b*]indoles with optical purity by the strategy of chiral resolution, which could serve as a complementary method to catalytic asymmetric approaches. This work will not only add new contents to the chemistry of Nazarov-type cyclization and indolylmethanols, but also contribute to the research field of constructing axially chiral indole-based scaffolds via asymmetric organocatalysis.

DECLARATIONS

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Authors' contributions

Performing the majority of the experiments: Wu P
Doing some of the experiments: Yan XY, Jiang S
Initially trying the model reaction: Lu YN
Co-directing this project and writing the draft manuscript: Tan W
Directing this project and revising the manuscript: Shi F

Availability of data and materials

Supplementary Materials are available online for this paper.

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The author declared that there is no conflict of interest.

Ethical approval and consent to participate
Not applicable.

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Not applicable.

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