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Communication

BF_3-promoted annulation of azonaphthalenes and ynamides for synthesis of benzo[*e*]indoles

Changwei Chen, Sunliang Cui*

College of Pharmaceutical Sciences, Zhejiang University, Hangzhou 310058, China

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ABSTRACT

A novel BF_3-promoted [3 + 2] annulation of azonaphthalenes and ynamides is described. This protocol provides a modular and efficient entry to functionalized amino benzo[*e*]indole derivatives smoothly.

Indole is a privileged structural motif of nitrogen containing heterocycles, and widely exists in many bioactive molecules like pharmaceuticals and agrochemicals [1–3]. Among them, 1-aminoindole derivatives exhibit important pharmacological properties, such as 5-HT_2 antagonists [4a], antioxidants [4b], diuretic agents [4c,d], ALDH1A1 inhibitors [4e–g], and potential therapeutic reagents for treatment of Alzheimer's disease [4h] (Fig. 1). However, the synthetic methods are nearly limited to transition-metal-mediated reactions [5]. Therefore, the efficient synthetic method to diverse functionalized 1-aminoindoles has received great attention in organic synthesis and medicinal chemistry.

In the course of finding suitable synthons, we particularly focused on the azonaphthalene scaffolds [6]. As we all know, azo group has been used as a directing group for many transformations *via*transition-metal-catalyzed C—H activation [7]. Meanwhile, the azo motif of azonaphthalenes could also work as an electron-withdrawing group to activate the aromatic rings for nucleophilic attack (Scheme 1). For example, Tan and co-workers reported a nice work of chiral phosphoric acid-catalyzed [3 + 2] annulation of azonaphthalenes with 2,3-disubstituted indoles to construct axially chiral benzo[*e*]indole derivatives [8] (Scheme 1a). Shi et al. reported another chiral phosphoric acid catalyzed [3 + 2] annulation of azonaphthalenes with 3-vinylindoles [9] (Scheme 1b). Wang also developed a *N*-heterocyclic carbene catalyzed tandem dearomatization/rearomatization reaction of azonaphthalenes and α-chloroaldehydes for assembly of chiral dihydrocinnolinone derivatives [10]. Recently, Li and co-workers have discovered a second-amine mediated [3 + 2] annulation of azonaphthalenes with aldehydes and ketones for synthesis of indole derivatives [11] (Scheme 1c). Therefore, azonaphthalenes are versatile building blocks for synthesis of nitrogen-containing heterocycles.

In continuation of our research in multicomponent reaction for heterocycle synthesis [12], we envisioned that ynamides might undergo cyclization with azonaphthalenes to deliver interesting heterocycles. Ynamides, a special type of alkynes, exihibit dual nucleophilic and electrophilic properties with carbon-carbon triple bonds attached to the nitrogen atom, which substitutes to electron-withdrawing groups [13]. Owing to their unique activities, ynamides have become popular in organic synthesis and have been reported to act as flexible synthons in cyclization by Hsung, Liu, Ye, Huang and other groups [14]. Our group also reported that ynamides could be used as C2 building blocks in cyclization with nitrile oxides [12f]. Herein, we would like to report a [3 + 2] annulation of azonaphthalenes and ynamides for modular and efficient entry to structurally divergent *N*-substituted benzo[*e*]indoles (Scheme 1d).

We commenced our study by investigating ynamide (**1a**) and azonaphthalene (**2a**) in the presence of 4 Å molecular sieve (MS) in DCM under argon, and BF_3-Et_2O (20 mol%) was used as catalyst (Table 1). However, no new product was observed when the reaction was performed at ambient temperature (entry 1). To our delight, a new product **3a** was detected and isolated in 36% yield while lowering the temperature to −20 °C (entry 2). The standard characterization including ^1H NMR, ^{13}C NMR and mass spectroscopy identified **3a** as a benzo[*e*]indole compound. And we further

* Corresponding author.
E-mail address: slcui@zju.edu.cn (S. Cui).

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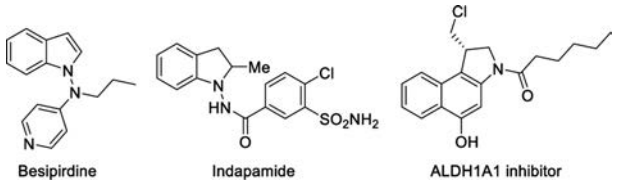
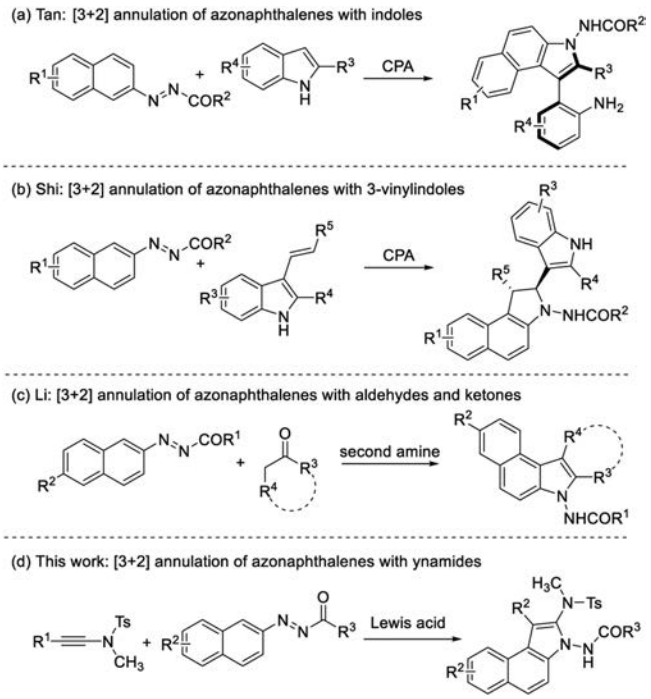
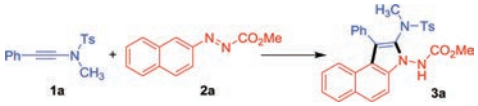


Fig. 1. Selected bioactive molecules containing 1-aminoindole unit.



Scheme 1. Annulation of azonaphthalene derivative.

Table 1
Optimization of reaction conditions.[a]



Entry	Solvent	Catalyst	Temp. (°C)	Yield (%)[b]
1	DCM	BF_3-Et_2O	25	–
2	DCM	BF_3-Et_2O	−20	36
3	DCE	CPA	80	–
4	DCE	AgOTf	80	–
5	DCE	$Sc(OTf)_3$	80	trace
6	DCE	$Cu(OTf)_2$	80	–
7	DCE	$Zn(OTf)_2$	80	–
8	DCE	$FeCl_3$	80	trace
9	DCM	BF_3-Et_2O	−78	60
10[c]	DCM	BF_3-Et_2O	−78	65
11[d]	DCM	BF_3-Et_2O	−78	90
12	Toluene	BF_3-Et_2O	−78	80
13	CH_3CN	BF_3-Et_2O	−40	84

CPA = 1,1′-binaphthyl-2,2′-diyl hydrogenphosphate.
[a] Reaction conditions: **1a** (0.3 mmol), **2a** (0.2 mmol), solvent (2 mL), 4 Å MS (50 mg), argon, then catalyst (20 mol%), 2 h. For experimental procedure, see the Supporting information.
[b] Yield refers to isolated product.
[c] BF_3-Et_2O (1 equiv.).
[d] BF_3-Et_2O (2 equiv.).

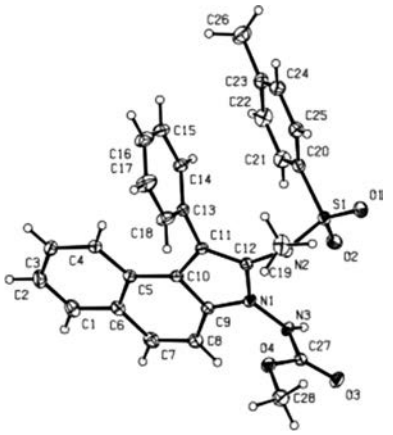
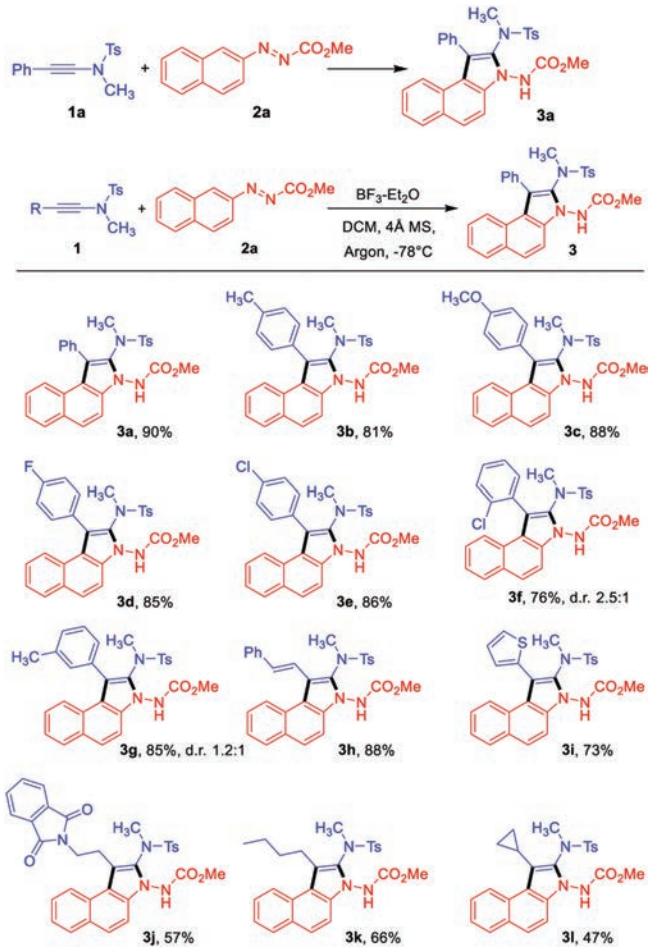


Fig. 2. Single crystal X-ray diffraction of **3a**.

confirmed the structure of **3a** by single-crystal X-ray diffraction analysis (CCDC: 1987024) (Fig. 2). For its structural details, see the Supporting Information. In addition, various Lewis acids such as CPA, AgOTf, $Sc(OTf)_3$, $Cu(OTf)_2$, $Zn(OTf)_2$ and $FeCl_3$ were also tested instead of BF_3-Et_2O. These reactions were carried out in DCE at 80 °C, but they were all found ineffective (entries 3-8), and only $Sc(OTf)_3$ and $Zn(OTf)_2$ could lead to trace amount of **3a**. Gratifyingly, decreasing the temperature to −78 °C could facilitate



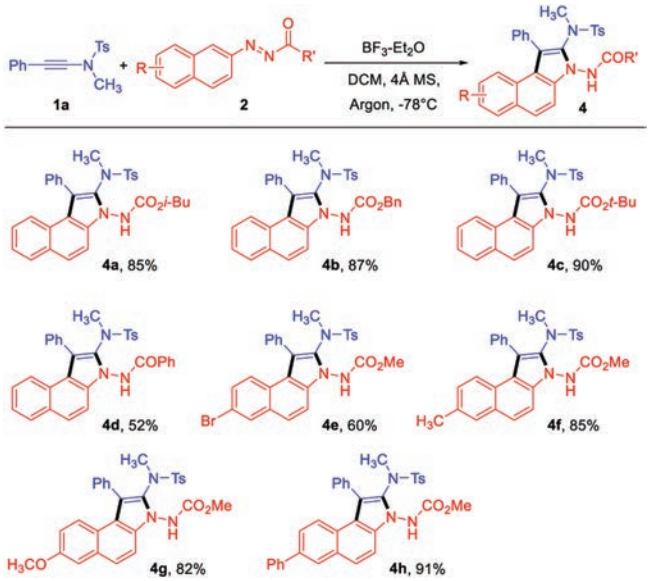
Scheme 2. Substrate scope of ynamides. Reaction conditions: **1** (0.3 mmol), (0.2 mmol), DCM (2 mL), 4 Å MS (50 mg), argon, then BF_3-Et_2O (2.0 equiv.), −78 °C, 2 h. Yield refers to isolated product. For experimental procedure and characterization data of products, see the Supporting information.

the reaction to improve the yield to 60% (entry 9). When the amount of BF_3-Et_2O was increased to 1 equiv., the yield of **3a** could be improved to 65% (entry 10), while using 2 equiv. of BF_3-Et_2O could further improve the yield to 90% (entry 11). The screening of solvents showed that toluene and CH_3CN were also effective, albeit with slightly lower yields (80% and 84%, entries 12 and 13).

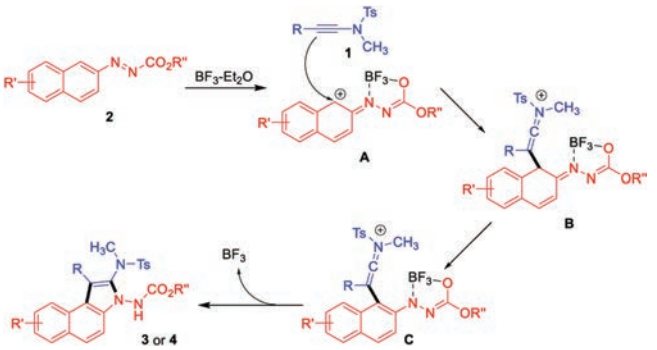
With the optimal reaction conditions in hand, we next examined the substrate scope of ynamides. As shown in Scheme 2, ynamides with electron-donating groups on the *para*-position of the aromatic ring could well engage in this process with azonaphthalene **2a** to deliver the corresponding products in excellent yields, such as methyl and methoxy (**3b** and **3c**). On the other hand, ynamides with electron-withdrawing groups like fluoro and chloro, were also tolerated to give the desired products **3d** and **3e**. In addition, *ortho*- and *meta*-substituents were applicable as well and did not show significant difference in yields compared to *para*-substituents (**3f** and **3g**). It should be noted that the reaction of *o*-chloro and *m*-methyl substitution at the phenyl ring of the ynamides furnished the products with *dr* values ranging from 2.5:1 to 1.2:1, probably due to the steric hindrance of the phenyl ring with the naphthalene ring. Moreover, the styrene containing ynamide was also compatible in this protocol to deliver **3h**. Heterocyclic ynamide could also participate well in this process to afford **3i** in good yield. Furthermore, when alkyl-substituted ynamides were employed, including *N*-protected amine moiety, butyl and cyclopropyl, the products could be obtained in moderate yields (**3j**-**3l**).

Furthermore, the generality of azonaphthalenes were also investigated. As shown in Scheme 3, a variety of azonaphthalene derivatives were amenable to this [3 + 2] annulation. When substituents R′ were alkoxyl groups, the corresponding products could be obtained in high yields (**4a**-**4c**). The reaction was applicable to azonaphthalene with benzoyl group to afford **4d** in moderate yields. The electronic nature and the substituents of the aromatic rings did not show significant effects on the reactivity (**4f**-**4h**), except for the bromo-substituted azonaphthalene with slightly lower yield (**4e**).

On the basis of these results and literatures [8,11,12], a plausible reaction mechanism was proposed in Scheme 4. Initially, the



Scheme 3. Substrate scope of azonaphthalenes. Reaction conditions: **1a** (0.3 mmol), **2** (0.2 mmol), DCM (2 mL), 4 Å MS (50 mg), argon, then BF-Et_2O (2.0 equiv.), −78 °C, 2 h. Yield refers to isolated product. For experimental procedure and characterization data of products, see Supporting information.



Scheme 4. Proposed mechanism.

azonaphthalene **2** could be activated by BF_3-Et_2O to deliver species **A**, which is added by electron rich ynamides to give intermediate **B**. The following isomerization furnishs the annulation products **3** or **4**. And the released BF_3 might coordinate with the amino group and equivalent amount of BF_3-Et_2O is necessary.

In conclusion, a novel [3 + 2] annulation of azonaphthalenes and ynamides has been developed to establish *N*-substituted benzo[*e*]indole derivatives in good to excellent yield. This process features a broad substrate scope and high efficiency.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.cclet.2020.04.010.

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