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Article

Lewis Acid-Catalyzed 1,3-Dipolar Cycloaddition of Bicyclobutanes with Isatogens: Access to Tetracyclic 2-Oxa-3-azabicyclo[3.1.1]heptanes

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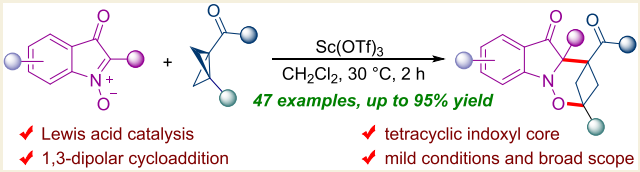
ABSTRACT: The 'escape from flatland' concept has gained significant traction in modern drug discovery, emphasizing the importance of three-dimensional molecular architectures, which serve as saturated bioisosteres of benzenoids. Bicyclo[1.1.0]butanes (BCBs), known for their high ring strain and numerous reactivities, offer a simple yet effective method for synthesizing these bicyclic frameworks. Although (3 + 2) annulations involving BCBs have been extensively studied, the 1,3-dipolar cycloaddition of BCBs leading to (3 + 3) annulation has received limited attention. Herein, we report the Lewis acid-catalyzed 1,3-dipolar cycloaddition of BCBs with isatogens allowing the synthesis of biologically relevant tetracyclic 2-oxa-3-azabicyclo[3.1.1]heptanes. Moreover, the reaction can be performed in a one-pot process by the in situ generation of isatogens from 2-alkynylated nitrobenzenes. Additionally, preliminary mechanistic and photophysical studies of the (3 + 3) annulated products and experiments toward the asymmetric version of this reaction are also provided.



KEYWORDS: *bicyclic scaffolds, (3 + 3) annulation, Lewis acid catalysis, strain release chemistry, nitrones, indoxyls*

INTRODUCTION

From several years, chemists have been enthralled by the concept of "escape from flatland", igniting significant interest and exploration. Traditionally, planar aromatic ring systems have been ubiquitous in drug discovery endeavors.[1−3] Thus, the utilization of C(sp^3)-rich three-dimensional (3D) scaffolds as bioisosteric replacements for planar aromatic ring systems has demonstrated remarkable benefits by replacing aromatic rings with saturated bicyclic frameworks.[4−7] The introduction of these saturated bicyclic frameworks not only influences the pharmacokinetic properties but also leads to enhanced potency, improved solubility, high lipophilicity, and increased metabolic stability of the resulting compounds.[1−3] Therefore, there is a resurgence of interest in developing synthetic methods for the efficient construction of these coveted 3D scaffolds. One of the prevalent strategies for the synthesis of bicyclic scaffolds is the utilization of bicyclo[1.1.0]butanes (BCBs) as the reactive precursors.[8−13]

Recently, the utilization of BCBs has gained prominence for constructing bicyclic scaffolds due to their remarkable reactivity, compact structure, and high strain energy (66.3 kcal/mol). BCBs enable the synthesis of a diverse range of bicyclic hydrocarbon scaffolds, facilitating the imitation of *ortho*-, *meta*-, and *para*-disubstitution patterns found in benzene derivatives (Scheme 1a).[8−16] One of the predominant modes of reactivity demonstrated by BCBs is their participation in cycloaddition reactions, facilitating the construction of intricate bicyclic scaffolds. The strain-release-driven (3 + 2) annulations have been the focal theme of research among these cycloaddition processes, particularly for their utility in synthesizing bicyclo[2.1.1]hexane structures. In this field, significant progress was made independently by Glorius and group[17] and Brown and group,[18] who discovered methods for intermolecular (3 + 2) annulation between alkenes and BCBs using photocatalysis. Adding to these advancements, Li and group[19] and Wang and group[20] demonstrated an innovative approach using a pyridine-boryl radical system to catalyze the formal (3 + 2) annulation of alkenes with BCBs.

Recent advances in BCB chemistry have primarily focused on photocatalysis- and radical-based methods. However, Lewis acid catalysis has emerged as a straightforward yet effective approach for facilitating annulations involving BCBs. Leitch and group pioneered this area by introducing Lewis acid catalysis for the formal (3 + 2) annulation between *N*-arylimines and BCBs, resulting in the formation of azabicyclo[2.1.1]hexanes (Scheme 1b).[21] Moreover, Studer and group applied a similar Lewis acid-catalyzed strategy to demonstrate the formal (3 + 2) annulation of ketenes with BCBs, resulting in bicyclo[2.1.1]hexanes, thus further expand-

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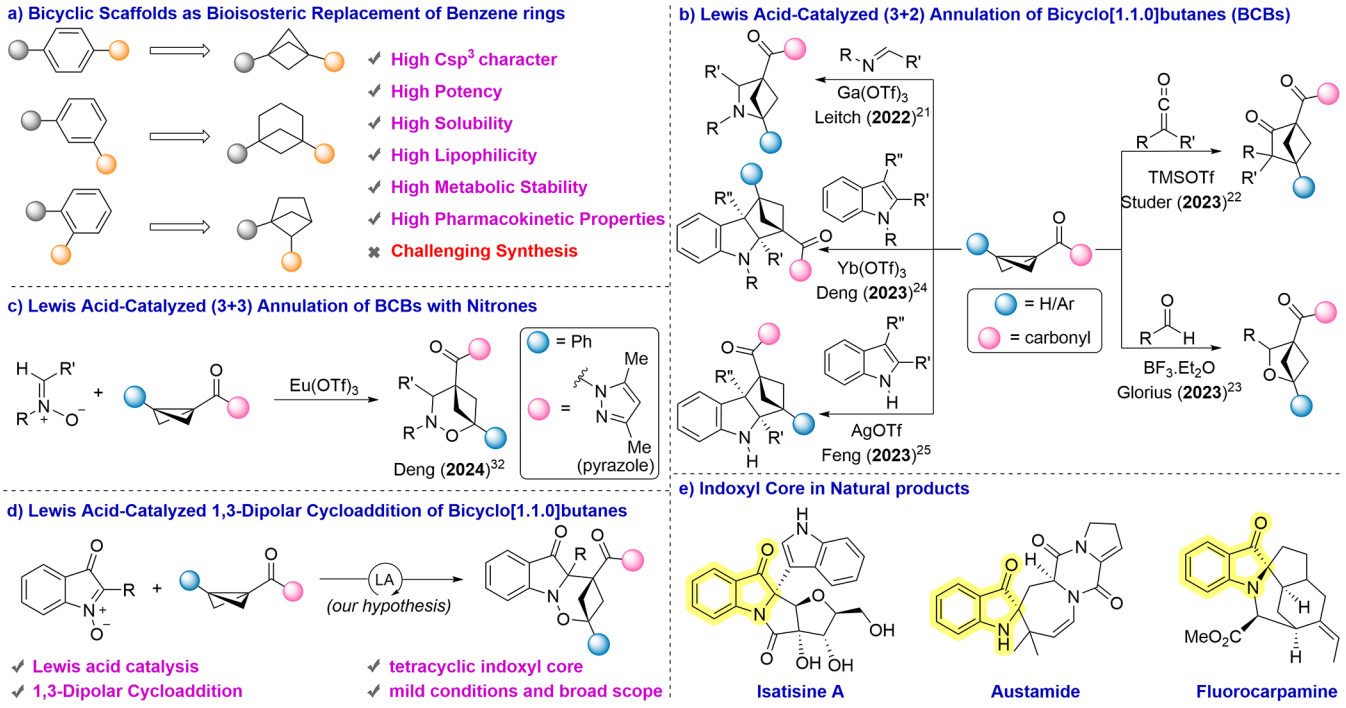
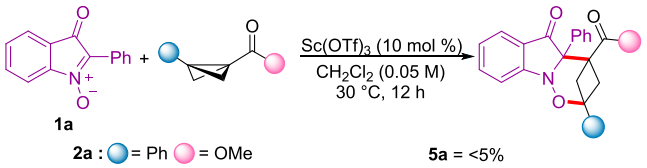
Scheme 1. Bicyclic Scaffolds as Benzene Bioisosters, BCBs in Cycloaddition Reactions, and Importance of the Indoxyl Core



ing the scope of this approach.[22] In addition, Glorius and group showed that aldehydes could also serve as coupling partners in the formal (3 + 2) annulation of BCBs.[23] In parallel developments, Deng and Feng independently reported the dearomative (3 + 2) annulation of indoles with BCBs, catalyzed by Lewis acids, to synthesize bicyclo[2.1.1]-hexanes.[24,25]

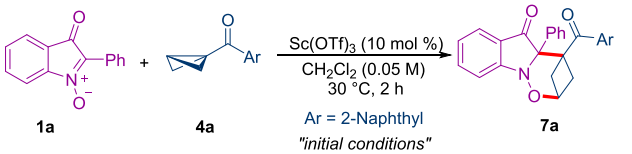
Scheme 2. Identification of the Suitable BCB Substrate



In addition to the (3 + 2) annulation of BCBs for the direct access to bicyclo[2.1.1]hexanes, strategies for the construction of bicyclo[3.1.1]heptane (BCHep) frameworks using BCBs under photocatalysis and Lewis acid catalysis have been known.[26−31] One of the effective approaches for the synthesis of BCHeps involves the reaction of 1,3-dipoles with BCBs. However, 1,3-dipolar cycloaddition with the central C−C bond of BCB for the synthesis of hetero-BCHeps has received only limited attention. One of the seminal reports, by Deng and co-workers,[32] describes a formal 1,3-dipolar cycloaddition between BCBs and nitrones (Scheme 1c).[32−40] It is worth noting that the heteroatom-incorporated bicyclic scaffolds often exhibit favorable properties compared to their all-carbon counterparts.[41,42] Consequently, there is growing interest among chemists in developing efficient methodologies for synthesizing these heteroatom-substituted bicyclic molecules.

While exploring suitable 1,3-dipoles, we encountered the utilization of isatogens as dipoles in dipolar cycloaddition reactions[43−45] and observed the tolerance under Lewis acid conditions.[46,47] Herein, we envisioned the Lewis acid-catalyzed 1,3-dipolar cycloaddition of isatogens with BCBs, a strategy that could furnish a variety of intricate tetracyclic indoxyl derivatives via a (3 + 3) annulation (Scheme 1d).[48−51] The significance of this approach is underscored by the prevalence of the indoxyl core in numerous natural alkaloids, many of which demonstrate a wide range of medicinal properties (Scheme 1e).[52−55] These structures have also found applications in fluorescence sensing technologies,[56] high-

Table 1. Optimization of the Reaction Conditions



entry	variation of the initial conditions[a]	yield of **7a** (%)[b]
1	none	77
2	$Yb(OTf)_3$ instead of $Sc(OTf)_3$	18
3	$Bi(OTf)_3$ instead of $Sc(OTf)_3$	28
4	$Cu(OTf)_2$ instead of $Sc(OTf)_3$	55
5	TfOH instead of $Sc(OTf)_3$	49
6	DCE instead of CH_2Cl_2	76
7	toluene instead of CH_2Cl_2	62
8	THF instead of CH_2Cl_2	11
9	1.5 equiv of **4a** instead of 1.2 equiv	86
10[c]	0 °C to rt instead of 30 °C	75
11[c]	5 mol % of $Sc(OTf)_3$	91(88)

[a]Initial conditions: **1a** (0.10 mmol), **4a** (0.12 mmol), $Sc(OTf)_3$ (10 mol %), CH_2Cl_2 (2.0 mL), 30 °C for 2 h. [b]The ^1H NMR yield of the crude products was determined using 1,3,5-trimethoxybenzene as the internal standard and the isolated yield was given in parentheses. [c]1.0 equiv of **1a**, 1.5 equiv of **4a**, CH_2Cl_2 (0.05 M).

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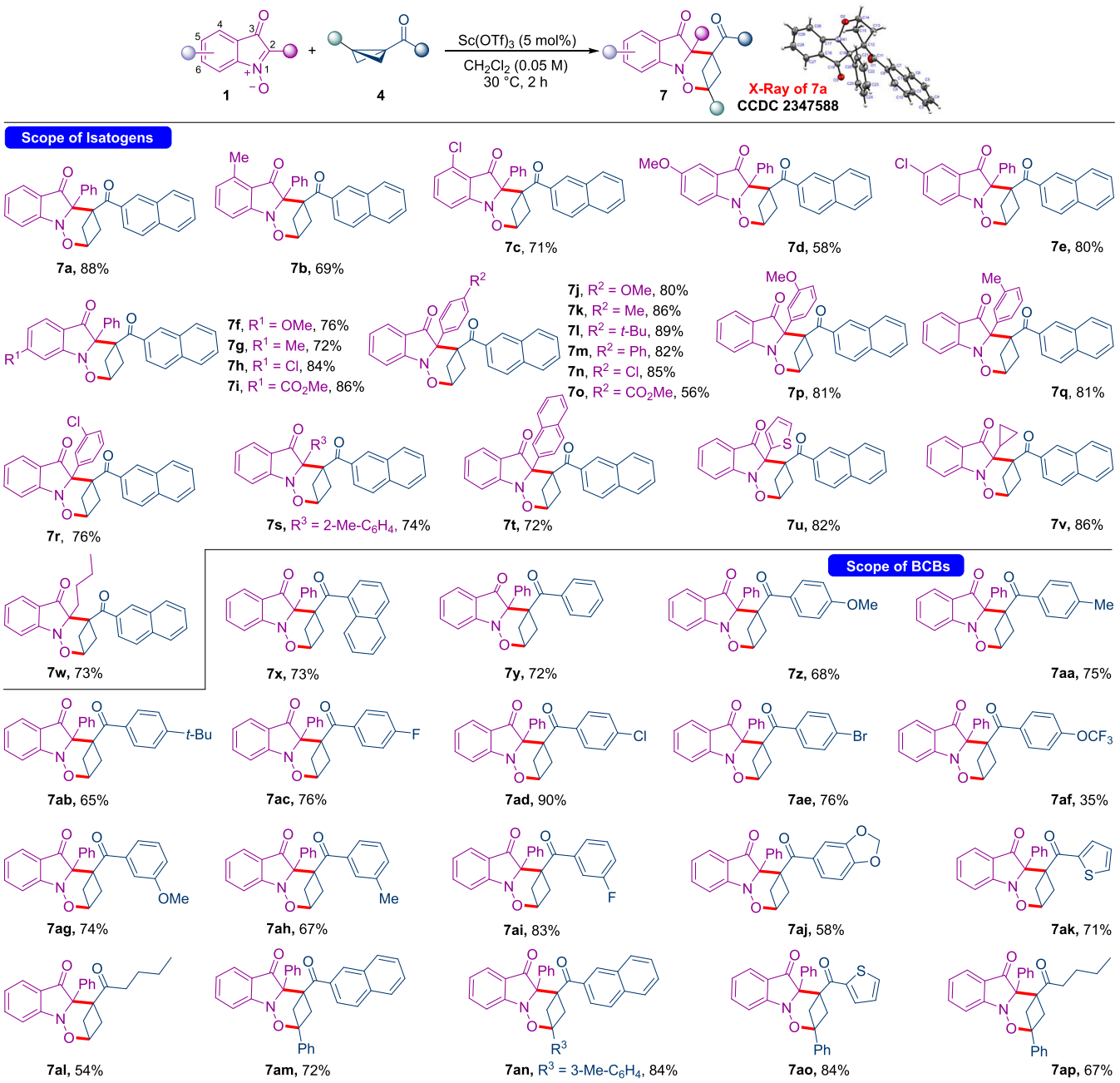
Scheme 3. Substrate Scope of the 1,3-Dipolar Cycloaddition of Isatogens with BCBs[a]



[a]General conditions: **1** (0.2 mmol), **4** (0.3 mmol, 1.5 equiv), $Sc(OTf)_3$ (5 mol %), CH_2Cl_2 (4.0 mL), 30 °C for 2 h. Yields of the isolated products are given.

lighting their versatility in both medicinal chemistry and materials science.

RESULTS AND DISCUSSION

The preliminary studies were focused on finding a suitable BCB substrate for this 1,3-dipolar cycloaddition. First, phenyl ester-substituted BCB **2a** was treated with the isatogen **1a** in the presence of $Sc(OTf)_3$ and CH_2Cl_2 as solvents (Scheme 2). However, the expected product **5a** did not form; instead, BCB was decomposed to the cyclobutene derivative. Then, phenyl ester BCB was changed to pyrazole-substituted BCB **3a**, but the desired product **6a** was still not formed. Interestingly, when pyrazole BCB was replaced with monosubstituted ketone BCB **4a**, the anticipated product **7a** was formed in 77% isolated yield. Hence, the optimization studies were then conducted using keto BCB **4a**.[57,58]

When the isatogen **1a** was treated with BCB **4a** in the presence of 10 mol % $Sc(OTf)_3$ and 2.0 mL of CH_2Cl_2 at 30 °C for 2 h, the desired product **7a** was obtained in 77% yield (Table 1, entry 1). Variations of the different Lewis acid catalysts did not enhance the yield of **7a** (Table 1, entries 2–4). Also, employing TfOH as the catalyst resulted in the formation of **7a** in 49% yield (Table 1, entry 5). The solvent screening indicated that DCE afforded **7a** in comparable yields, while toluene and THF furnished **7a** in reduced yields (entries 6–8). When the reaction was performed using 1.5 equiv of **4a**, the product **7a** was formed in an improved yield of 86% (entry

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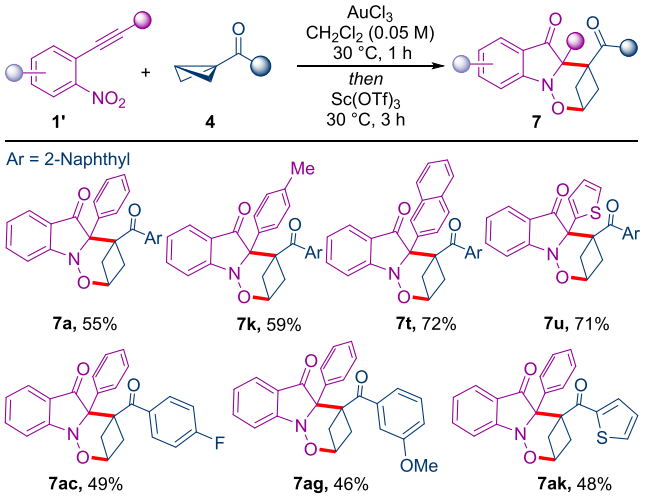
9). Notably, initiating the reaction at 0 °C and then warming to 30 °C was not helpful (entry 10). Interestingly, performing the reaction using 5 mol % $Sc(OTf)_3$ instead of 10 mol % afforded the desired product **7a** in 91% yield (entry 11). It is likely that a higher concentration of $Sc(OTf)_3$ leads to the conversion of BCB to the cyclobutene derivative. Hence, entry 11 was taken as the optimized condition, which was used for the substrate scope evaluation.[59,60]

With the identified reaction conditions in hand, the substrate scope of this 1,3-dipolar cycloaddition reaction of isatogens with BCBs was investigated. Initially, we examined the compatibility of various isatogen derivatives **1** with BCB **4a** (Scheme 3). Isatogens bearing different substitutions at the 4- and 5-positions of the benzene ring demonstrated efficacy under the optimized conditions, affording moderate to good yields of the tetracyclic indoxyl products (**7a**–**7e**). The structure of **7a** was confirmed by X-ray analysis of the crystals.[61] Various isatogens possessing electron-releasing, electron-neutral, or electron-withdrawing groups at the 6-position of the ring reacted well to give the anticipated products in good yields (**7f**–**7i**). Subsequently, we investigated the influence of the aryl moiety at the 2-position of isatogen. Isatogens with various *para*-substituted aryl moieties at the 2-position proved to be viable substrates under the present conditions, yielding the desired products in moderate to high yields (**7j**–**7o**). Both *meta*- and *ortho*-substituted aryl moieties were smoothly engaged in the 1,3-dipolar cycloaddition, delivering the expected products in good yields (**7p**–**7s**). In addition, not only the phenyl moiety but also the 2-naphthyl- and 2-thienyl-derived isatogens delivered the anticipated product in good yield (**7t, 7u**). Furthermore, the presence of alkyl substitution at the 2-position of the isatogen did not alter the product formation (**7v, 7w**).

The scope of the reaction was then explored by employing variously substituted BCBs such as **4**. In addition to 2-naphthyl-substituted keto BCB **4a**, 1-naphthyl-substituted BCB also furnished the 1,3-dipolar cycloadduct **7x** in 73% yield. Various keto-containing BCBs, featuring substitutions at *para*- and *meta*-positions on the phenyl ring, demonstrated effectiveness as substrates for this (3 + 3) annulation reaction (**7y**–**7ai**). Moreover, keto BCBs with a disubstituted aryl moiety or heteroaryl ring afforded the tetracyclic indoxyl product in good yields (**7aj, 7ak**). Furthermore, butyl-substituted BCB also yielded the desired cycloaddition product **7al** in 54% yield. Gratifyingly, when the reaction was performed with 1,3-disubstituted BCB ketones bearing aryl and alkyl moieties, the (3 + 3) annulation products were formed in good yields (**7am**–**7ap**), thus expanding the scope of the present 1,3-dipolar cycloaddition.

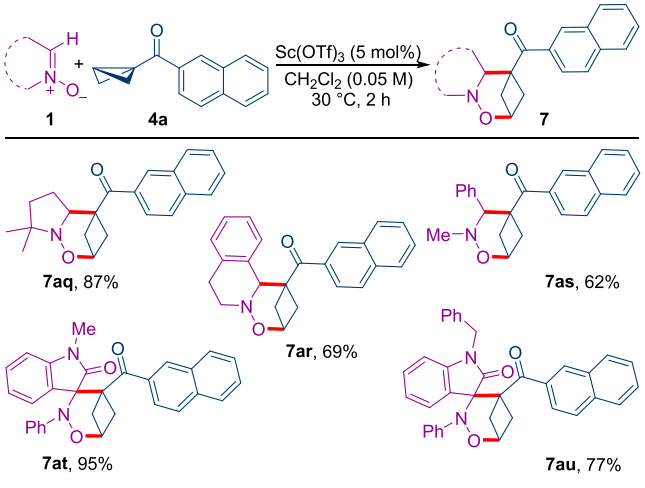
Interestingly, this Lewis acid-catalyzed 1,3-dipolar cycloaddition of BCB can also be done using a one-pot strategy; thereby, the need to isolate the isatogen substrates can be avoided. The isatogens are typically prepared from the Au-catalyzed cycloisomerization of 2-nitroalkynes **1′** and are known for their in situ trapping in cycloaddition reactions.[43−45,62,63] This one-pot process allows direct access to tetracyclic indoxyl derivatives from 2-nitroalkynes **1′** employing BCBs **4** (Scheme 4). When nitroalkyne **1a′** was treated with BCB **4a** under the one-pot reaction conditions, the corresponding tetracyclic product **7a** was formed in 55% yield. Thereafter, the differently substituted 2-nitroalkynes were examined, and in all cases, the reaction furnished the desired (3 + 3) product in moderate yields (**7k, 7t, 7u**). Later, this one-pot strategy was extended with the variation on BCBs with electronically different aryl groups, and in all cases, the corresponding target tetracyclic indoxyl products were formed in moderate yields (**7ac, 7ag, 7ak**).

Scheme 4. Reaction of In Situ-Generated Isatogens with BCBs



This 1,3-dipolar cycloaddition involving BCB is not only limited to isatogens as 1,3-dipoles but can also be extended to other cyclic nitrones, which performed well under the optimized reaction conditions to give the anticipated products in good yields (**7aq, 7ar**) (Scheme 5). Also, the acyclic nitrone delivered the desired (3 + 3) annulation product **7as** in 62% yield. Moreover, the isatin-derived keto-nitrones also reacted with BCB **4a** under the optimized conditions to furnish the desired (3 + 3) annulated products **7at** and **7au** in 95 and 77% yields, respectively.

Scheme 5. Reaction with Other Cyclic/Acyclic Nitrones



Given the fact that BCBs are a distinct class of donor−acceptor (D−A) cyclopropanes with a significantly higher strain energy compared to typical D−A cyclopropanes (27 kcal/mol), they often display similar reactivity to D−A cyclopropanes in many reactions.[64−68] To explore this similarity, an intermolecular competition experiment was conducted between BCB **4a** and cyclopropane **8a** with the isatogen **1a** under Lewis acid conditions (Scheme 6). When

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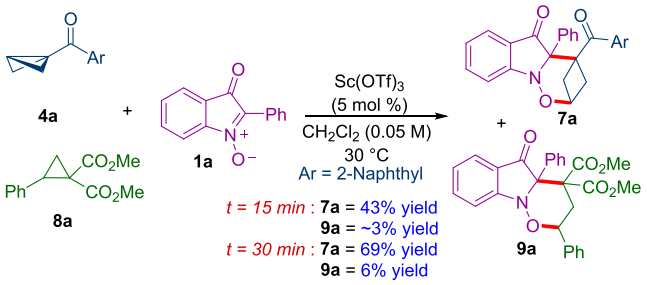
Scheme 6. Competition Experiment between BCB and DA-Cyclopropane



the reaction was performed under optimized conditions and quenched after 15 min, the (3 + 3) annulated product **7a** from BCB **4a** was obtained in 43% yield, while the product **9a** from D−A cyclopropane **8a** was formed in only ∼3% yield. After 30 min, the yields of **7a** and **9a** were 69 and 6%, respectively. These findings demonstrate that BCBs react ∼10 times faster than D−A cyclopropanes when treated with isatogens, likely due to their higher strain energy.

Moreover, to examine the substituent effect for this 1,3-dipolar cycloaddition reaction, a Hammett analysis[69] was done by calculating the reaction rates for individual substrates with different *para*-substituents on the aryl moiety present at the 2-position of isatogen (Figure 1a). Kinetic studies revealed that isatogens bearing 4-OMe or 4-Me groups at the aryl moiety at the 2-position react faster than the 4-CO_2Me- or 4-Cl-substituted ones. A negative linear correlation was observed when $\log(k_X/k_H)$ was plotted against σ, indicating a linear free-energy relationship (ρ = −0.6). This study likely is an indication that a positive charge was formed in the transition state during the cycloaddition process. A related negative correlation was observed recently by Zheng and co-workers in the reaction of BCBs with vinyl azides.[30]

Considering the potential of indoxyl-core-containing compounds in fluorescence sensing applications,[56] we explored the photophysical properties of selected indoxyl-fused bicyclo[3.1.1]heptane derivatives (Figure 1b−d). These compounds exhibited significant fluorescence in $CHCl_3$ under 365 nm ultraviolet (UV) light irradiation. The UV−visible (UV−vis) absorption and emission spectra of these compounds in $CHCl_3$ revealed that varying the substituent patterns on such tetracyclic indoxyl derivatives allowed fine-tuning of the corresponding emission maximum wavelengths.

To showcase the synthetic application of the present methodology, scale-up synthesis and synthetic transformations of **7a** were carried out (Scheme 7). The tetracyclic indoxyl derivative **7a** was obtained in 87% yield through the 1,3-dipolar cycloaddition reaction performed on 2.0 mmol, demonstrating the scalability of the present reaction. Treatment of **7a** with $LiAlH_4$ resulted in the reduction of both keto groups to afford secondary alcohol containing the tetracyclic indoxyl derivative **10a** in 63% yield as a single diastereomer. Selective monobromination of the carbocyclic ring of indoxyl **7a** was accomplished using *N*-bromo succinimide (NBS) under mild conditions to afford the bromo derivative **11a** in 92% yield. Interestingly, hydrogenation of **7a** using H_2 gas in the presence of Pd/C led to the cleavage of the N−O bond, yielding the trisubstituted cyclobutane derivative **12a** in 71% yield as a single diastereomer. Treatment of **12a** with an aryne generated from the triflate precursor **13** using KF and 18-crown-6 resulted in a smooth *O*-arylation to furnish **14a** in 59% yield.

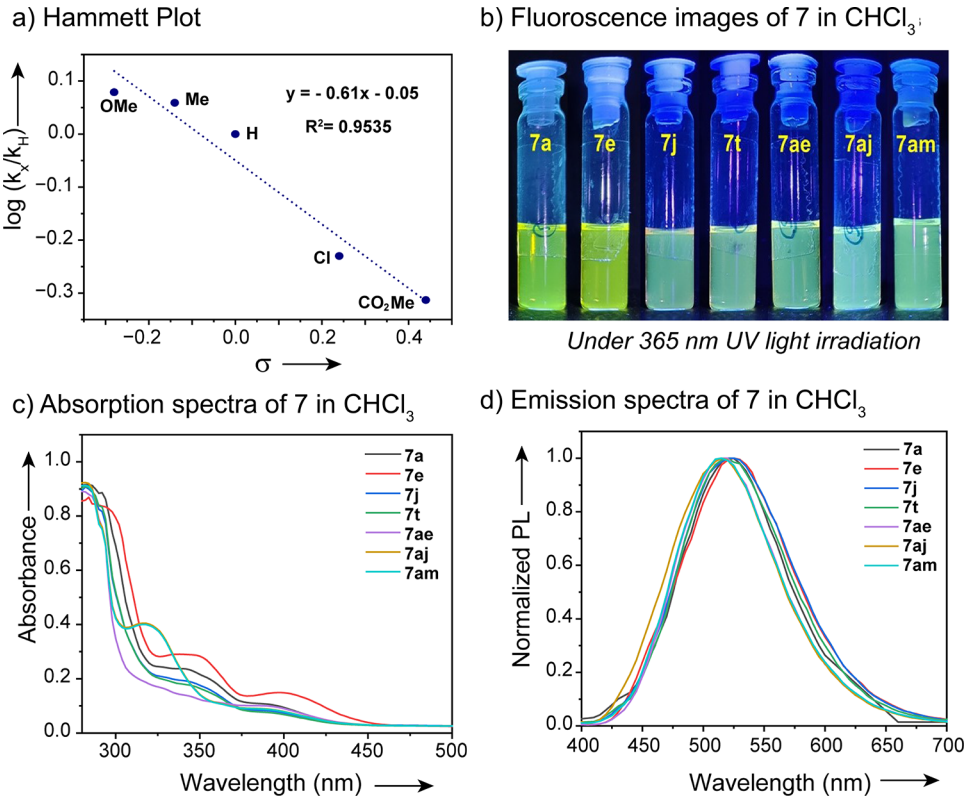


Figure 1. Hammett analysis and photophysical studies.

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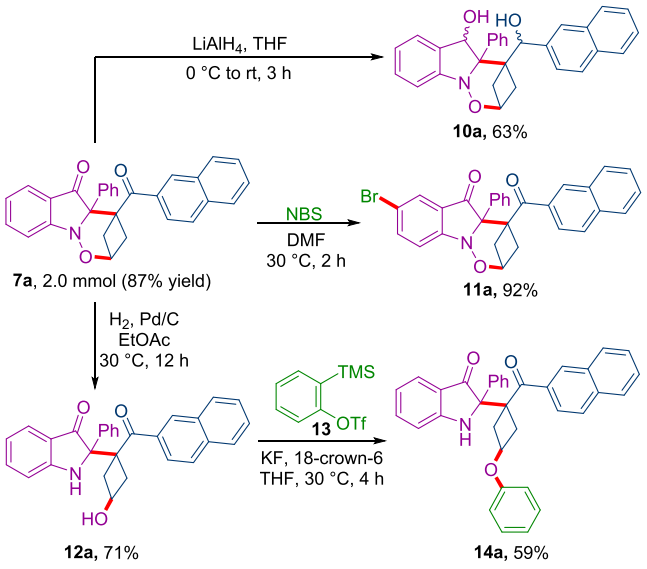
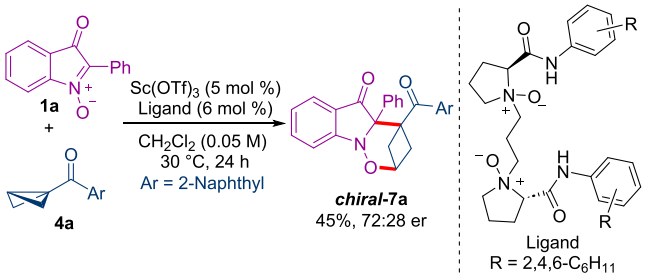
Scheme 7. Scalable Reaction and Synthetic Transformations



Subsequently, attempts were made to develop an asymmetric version of this newly established 1,3-dipolar cycloaddition. Given the utilization of *N*-oxide ligands with Lewis acids in asymmetric catalysis,[65,66] experiments were performed to develop the asymmetric (3 + 3) annulation. Initially, when the isatogen **1a** was treated with BCB **4a** in the presence of $Sc(OTf)_3$ and the cyclohexyl amine-derived *N*-oxide ligand, the expected tetracyclic indoxyl product **7a** was obtained in 45% yield with a 72:28 enantiomer ratio (er) (Scheme 8). Further attempts to improve the yield and enantioselectivity of the tetracyclic indoxyl product were unsuccessful.

Scheme 8. Initial Results on Enantioselective 1,3-Dipolar Cycloaddition



CONCLUSIONS

In conclusion, we have demonstrated the Lewis acid-catalyzed 1,3-dipolar cycloaddition of BCBs with isatogens, resulting in the formation of biologically significant tetracyclic indoxyl derivatives.[70] The reaction is operationally straightforward, proceeds smoothly under mild conditions, and shows good functional group compatibility with a broad scope. The versatility of this methodology can be extended to other cyclic and acyclic nitrones. Additionally, the reaction was successfully carried out from 2-nitroalkynes and BCBs in a one-pot process. Preliminary studies toward asymmetric 1,3-dipolar cycloaddition were also performed. Product functionalizations were carried out to illustrate the synthetic utility of this methodology. Efforts to further increase the enantioselectivity of the asymmetric 1,3-dipolar cycloaddition are currently ongoing in our laboratory.

METHODS

General Procedure for the Lewis Acid-Catalyzed 1,3-Dipolar Cycloaddition of BCBs with Isatogens

To an oven-dried screw-capped test tube equipped with a magnetic stir bar, $Sc(OTf)_3$ (0.005 g, 0.01 mmol) was added inside the glovebox. Then, isatogens **1** (0.2 mmol) and 4.0 mL of CH_2Cl_2 were added outside the glovebox under a nitrogen atmosphere. After that, BCBs **4** (0.3 mmol) were added. Then, the reaction mixture was stirred for 2 h at 30 °C. After 2 h, the solvent was evaporated under reduced pressure, and the crude residue was preadsorbed on silica gel and purified by flash column chromatography on silica gel (petroleum ether-EtOAc as the eluent) to afford **7** in good to excellent yields.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacsau.4c00839.

Details on experimental procedures, characterization data, and NMR spectra of all of the 2-oxa-3-azabicyclo[3.1.1]heptanes (PDF)

Crystal data of **7a** (CIF)

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Notes

The authors declare no competing financial interest.

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