Access to Spiro-bicyclo[2.1.1]hexanes via BF_3·Et_2O-Catalyzed formal [2π + 2σ] cycloaddition of Bicyclo[1.1.0]butanes with Benzofuran-derived Oxa(aza)dienes

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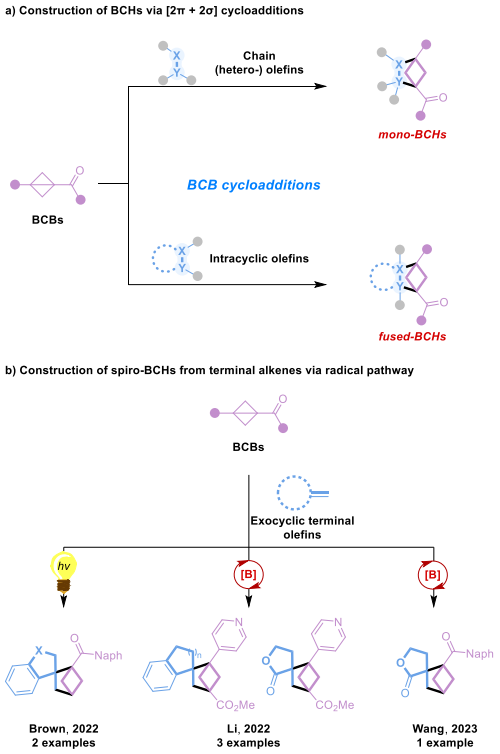
KEYWORDS: dipolar cycloaddition, bicyclo[1.1.0]butanes, strained molecules, bicyclic compounds, spirocycles

ABSTRACT: Herein, we have developed a method for the construction of spiro[benzofuran-2,2'-bicyclo[2.1.1]hexanes] via BF_3·Et_2O-catalyzed formal [2π + 2σ] cycloaddition of bicyclo[1.1.0]butanes with benzofuran-derived oxa(aza)dienes. This transformation allowed for facile access to a variety of functionalized spiro-bicyclo[2.1.1]hexanes in good yields (up to 99% yield) with excellent regioselectivities and a broad substrate scope (34 examples) under mild reaction conditions. Moreover, the synthetic utility of the cycloadducts were further emphasized through a scale-up experiment and subsequent synthetic transformations.

The scholarly interest in recent decades has been considerable towards the paradigm shift of substituting planar arene moieties with three-dimensional (3D) saturated bicyclic analogues, a concept popularly referred to as "escape from flatland".[1] Among those 3D skeletons, bicyclo[2.1.1]hexanes (BCHs) have captured the focus of synthetic chemists due to their utility as bioelectronic substitutes for *ortho*- or *meta*-substituted arenes to enhance both the physicochemical and pharmacokinetic profiles of bioactive drugs.[2] There has been a heightened emphasis on formulating efficient synthetic methodologies for BCHs,[3] and the [2π + 2σ] cycloaddition of bicyclo[1.1.0]butanes (BCBs)[4] with 2π-synthons emerges as a notable synthetic strategy due to its broad substrate compatibility and effectiveness.[5-7] Blanchard pioneered this approach in 1966 with the inaugural application of thermally driven [2π + 2σ] cycloadditions of BCBs with alkenes to yield captivating mono-BCHs.[5a] Very recently, the [2π + 2σ] cycloadditions[6] via radical pathway between BCBs and alkenes were flourished, pioneered by Glorius[6a] and Brown[6b]. Furthermore, Leitch's[7a] study on the Lewis acid catalyzed cycloaddition of imines and BCBs led to a rapid development of the [2π + 2σ] dipolar cycloadditions.[7] These aforementioned elegant works provided a variety of mono- or fused-BCHs (Scheme 1a). Despite the widespread usage of spirocycles in bioactive natural and synthetic compounds,[8] the synthesis of BCHs incorporating spirocycles has been constrained. Brown[6b] reported the pioneering synthesis of two examples of spiro-BCHs in 2022 through photoinduced cycloaddition with BCBs and 1,1-disubstituted alkenes. Subsequently, Li[6d] reported three cases of constructing spiro-BCHs from pyridine BCBs through the selective activation of remote bonds catalyzed by diboron compounds, while Wang[6h] also employed a similar strategy to achieve the synthesis of a spiro-BCH (Scheme 1b). These protocols for spiro-BCHs features exocyclic terminal olefins as 2π-partner and radical cycloaddition pathway. Considering spirocycles bearing unique rigidity and three-dimensional configuration could lead to potential biological properties,[9] developing [2π + 2σ] cycloaddition reactions of BCBs to furnish the valuable diversity spiro-BCHs with diverse structure is still highly demanded.

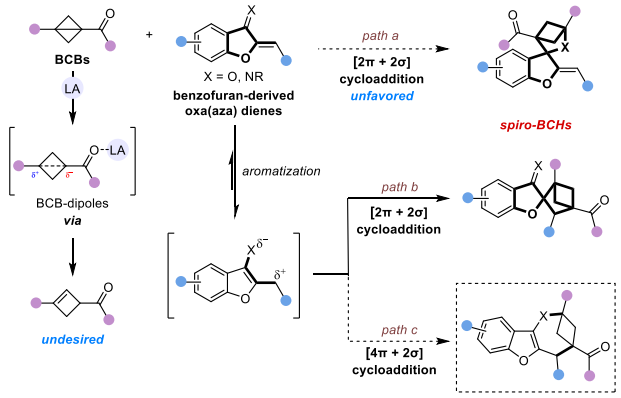
Scheme 1. Construction of BCHs from BCBs



Recently, we reported a Lewis acid-catalyzed [4π + 2σ] cycloaddition of BCBs with nitrones, providing the novel hetero-BCHeps.[10] Hence, we speculated that the intended spiro-BCHs may also be achieved via the Lewis acid catalyzed dipolar cycloaddition of BCBs with particular 2π-

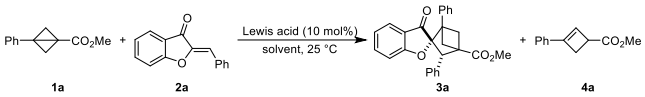
partners. The benzofuran-derived oxa(aza)dienes, which were widely utilized in the synthesis of the important benzofuran-incorporated heterocycles,[11] may serve as the ideal choice for constructing desired spiro-BCHs which incorporated the potentially bioactive benzofuran units.[12] To realize the transformation, several issues should be concerned. It is noteworthy that the Lewis acid catalyzed dipolar cycloadditions of BCBs with *α,β*-unsaturated compounds have not been reported, which presumably caused by the mismatch between in-situ formed BCB-dipole and 2π-partner. Consequently, choosing either a suitable Lewis acid catalyzed system and 2π-partner is crucial in matching the reactivity of BCB dipoles and electron-deficient oxa(aza)dienes. Besides, the Lewis acid catalyzed dipolar [2π + 2σ] reactions of BCBs with imines or ketones have been realized by Leitch[7a] and Glorius[7b], indicating the imine or ketone units of oxa(aza)dienes may react with BCBs which leading to complex chemoselectivity in the reaction. We inferred that this pathway is unfavored due to the potential aromatization driving force of benzofuran-derived oxa(aza)dienes (path a), although this property also may lead to the generation of undesired [4π + 2σ] product (path c). Additionally, the formation of cyclobutenes from BCBs is also a potential side reaction and needs to be inhibited. Herein, we report a formal [2π + 2σ] cycloaddition of BCBs with benzofuran-derived oxa(aza)dienes promoted by Lewis acids, providing a series of novel spiro-BCHs with a broad substrate scope (Scheme 2).

Scheme 2. BF_3-catalyzed formal [2π + 2σ] cycloaddition of benzofuran-derived oxa(aza)dienes with BCBs for synthesis of spiro-BCHs



We initiated our studies by employing bicyclo[1.1.0]butane **1a** (0.20 mmol, 2.0 equiv.) and benzofuran-derived oxadiene **2a** (0.10 mmol, 1.0 equiv.) as model substrates in the presence of $BF_3{\cdot}Et_2O$ (0.01 mmol, 10 mol%) in toluene (2.0 mL) at 25 °C (Table 1, entry 1). Gratifyingly, the desired spiro-BCH **3a** was obtained in 54% yield, and **2a** was recovered in a yield of 29%. Simultaneously, the decomposition product cyclobutene **4a** derived from BCB **1a** was obtained in 67% yield. Encouraged by the result, various Lewis acids were assessed to improve the conversion of **2a** and reduce the formation of cyclobutene. Most selected Lewis acids demonstrated inefficacy in producing the target product **3a** (entries 2-10). Among them, $Eu(OTf)_3$, $Er(OTf)_3$, $Ni(OTf)_2$,

Table 1. Optimization of the Reaction Conditions[a]



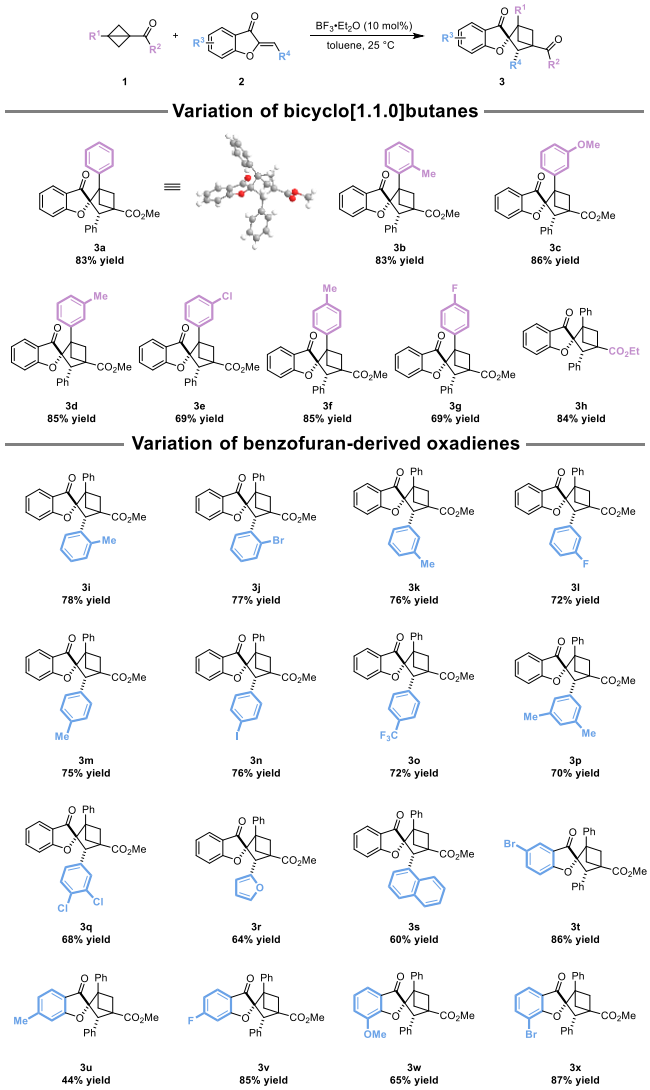
Entry	Lewis acid	Solvent	Yield of **3a** (%)[b]	Yield of **4a** (%)[b]	Recovery of **2a** (%)[b]
1	$BF_3{\cdot}Et_2O$	toluene	54	67	29
2	TMSOTf	toluene	-	92	96
3	$Ga(OTf)_3$	toluene	-	91	96
4	$Sc(OTf)_3$	toluene	-	87	97
5	$Bi(OTf)_3$	toluene	-	88	95
6	$Eu(OTf)_3$	toluene	-	-	95
7	$Er(OTf)_3$	toluene	-	-	97
8	$Ni(OTf)_2$	toluene	-	-	96
9	$Zn(OTf)_2$	toluene	-	-	94
10	$Yb(OTf)_3$	toluene	-	< 5	95
11	$In(OTf)_3$	toluene	< 5	85	92
12	AgOTf	toluene	23	75	67
13	$BF_3{\cdot}Et_2O$	THF	-	82	91
14	$BF_3{\cdot}Et_2O$	DMF	-	85	90
15	$BF_3{\cdot}Et_2O$	CH_2Cl_2	21	81	54
16	$BF_3{\cdot}Et_2O$	EtOAc	36	72	43
17	$BF_3{\cdot}Et_2O$	MeCN	14	83	70
18[c]	$BF_3{\cdot}Et_2O$	toluene	56	64	30
19[d]	$BF_3{\cdot}Et_2O$	toluene	83	62	-
20[e]	$BF_3{\cdot}Et_2O$	toluene	-	-	98
21	-	toluene	-	-	99

[a] Reaction conditions: **1a** (0.20 mmol), **2a** (0.10 mmol), Lewis acid (0.01 mmol, 10 mol%), solvent (2.0 mL), N_2 atmosphere, 25 °C, 10 mins. [b] Isolated yield. [c] toluene (1.5 mL) and the solution of **1a** (0.40 M in toluene, 0.20 mmol) was added dropwise within 5 mins. [d] with **1a** (0.30 mmol). [e] with 20 mol% H_2O. Abbreviation: THF = tetrahydrofuran, DMF = *N*,*N*-dimethylformamide.

and $Zn(OTf)_2$ failed to cleave the ring of BCB **1a** even the reaction time was extended to 24 hours (entries 6-9). The utilization of $In(OTf)_3$ and AgOTf gave inferior outcomes (<5% yield, 23% yield) (entries 11-12). Consequently, $BF_3{\cdot}Et_2O$ demonstrated optimal reactivity. Subsequently, other solvents were also examined, but lower yields of **3a** were obtained (entries 13-17), ultimately highlighting toluene as the preeminent solvent. Furthermore, the slow addition of **1a** to the reaction mixture gave a comparable result (Table 1, entry 18), while the retrieval of **2a** was sustained at a 30% yield. Elevating the loading of bicyclo[1.1.0]butane **1a** from 0.20 mmol to 0.30 mmol resulted in the formation of **3a** with an 83% yield, accompanied by the complete conversion of **2a** (Table 1, entry 19). However, the reaction was impeded in the presence of 20 mol% water (entry 20). Notably, no [2π + 2σ] product which was generated via ketone unit and [4π + 2σ] product were detected during the process of condition screening. Control experiment showed that the Lewis acid catalyst is crucial for this transformation (Table 1, entry 21). Ultimately, the optimum conditions identified were based on the use of bicyclo[1.1.0]butanes **1** (3.0 equiv.), benzofuran-derived oxadienes **2** (1.0 equiv.) in toluene (0.05 M) at 25 °C in the presence of $BF_3{\cdot}Et_2O$ (10 mol%).

Upon establishing the optimized reaction conditions, an exploration of the substrate scope was undertaken. First, various BCBs **1** were reacted with benzofuran-derived oxadiene **2a**. As summarized in Table 2, BCBs **1b-1d, 1f**

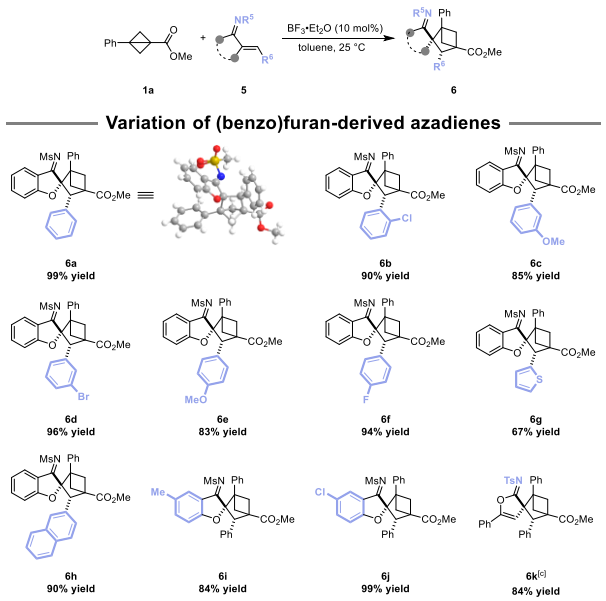
Table 2. Substrate scope investigation[a] [b]



[a] Reaction conditions: **1** (0.60 mmol), **2** (0.20 mmol), $BF_3{\cdot}Et_2O$ (0.02 mmol, 10 mol%), toluene (4.0 mL), N_2 atmosphere, 25 °C. [b] isolated yields.

bearing electron-donating groups (*o*-Me, *m*-OMe, *m*-Me, *p*-Me) furnished the corresponding products (**3b-3d, 1f**) in high yields (83%-86%). However, BCBs **1e** and **1g** bearing electron- withdrawing groups (*m*-Cl, *p*-F) reduced the yields (69%). Notably, the BCB substituted with *p*-CF_3 only provided a trace amount of the desired product. Moreover, ethyl substituted BCB **1h** can also maintain high yield (84%). Apart from BCB esters, *N*,*N*-dimethyl-3-phenylbicyclo[1.1.0]butane-1-carboxamide, monosubstituted BCB sulfones and monosubstituted BCB ketone were evaluated, but no reaction occurred. Moreover, disubstituted BCB ketone and BCB containing an acyl pyrazole group gave complex reaction mixtures. (details were shown in Supporting Information). Attention was then paid to the benzofuran-derived oxadienes. An array of benzofuran-derived oxadienes **2b-2h**, bearing either electron-donating or electron-withdrawing groups on the *ortho* (*o*-Me, *o*-Br), *meta* (*m*-Me, *m*-F), and *para* positions (*p*-Me, *p*-I, *p*-CF_3) of phenyl rings (R^4), gave products in good yields (**3i-3o**, 72%-78% yields). It was noteworthy that 3,5-diMe and 3,4-diCl substituted substrates **2i** and **2j** underwent the reaction smoothly, affording the target products **3p** (70% yield) and **3q** (68% yield), respectively. Benzofuran-derived oxadienes **2k** and **2l**, featuring a heteroaryl R^4 group (2-furyl) and a fused-ring R^4 group (*α*-naphthyl), also reacted smoothly, producing **3r** and **3s** with yields of 64% and 60%. However, benzofuran-derived oxadiene with aliphatic R^4 group (cyclohexyl) gave a complex reaction mixture (details were shown in Supporting Information). The influence of the R^3 group on the benzofuran-derived oxadienes was also investigated, the reactions of benzofuran-derived oxadienes **2m, 2o-2q** bearing various substituents (5-Br, 6-F, 7-OMe and 7-Br) of the benzofuran ring also effciently proceeded to afford the target products **3t, 3v-3x** in 65-87% yields. It is worth noting that the methoxyl group on the C6 position failed to give the desire product and BCB **1a** was completely decomposed into cyclobutene (details were shown in Supporting Information). Nevertheless, the **2n** bearing a methyl group at the C6 position could engage in the reaction to produce **3u**, albeit with reduced yield (44%). The structure of **3a** was unambiguously determined *X*-ray single crystal diffraction, and the configurations of other products were assigned by analogy.

Table 3. (benzo)furan-derived azadienes scope investigation[a] [b]

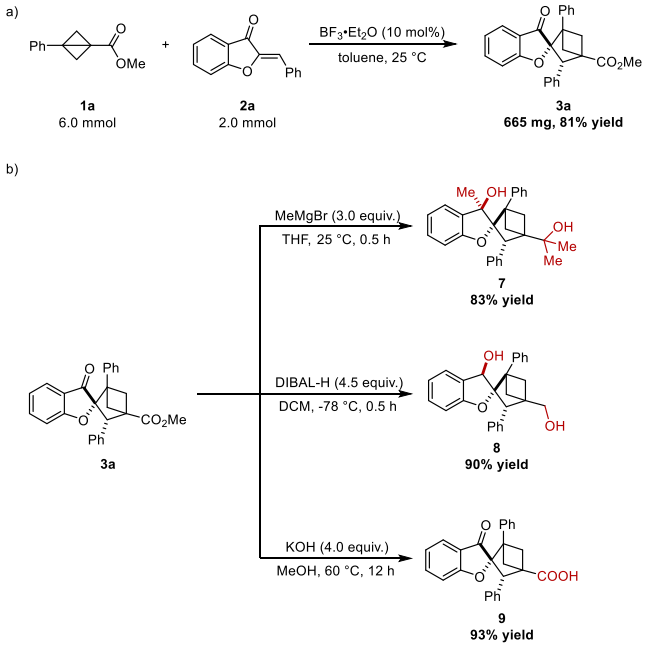


[a] Reaction conditions: **5** (0.20 mmol), $BF_3{\cdot}Et_2O$ (0.02 mmol, 10 mol%), toluene (3.0 mL), the solution of **1a** (0.30 M in toluene, 0.30 mmol) was added dropwise within 5 mins, N_2 atmosphere, 25 °C. [b] isolated yields. [c] **1a** (0.40 mmol), **5** (0.20 mmol), $BF_3{\cdot}Et_2O$ (0.02 mmol, 10 mol%), toluene (4.0 mL), N_2 atmosphere, 25 °C.

Apart from benzofuran-derived oxadienes, the benzofuran-derived azadienes are also evaluated. With the simple adjustment of feeding method and substrate equivalent, target product **6a** could be obtained in excellent yield (99%) under the optimized conditions, indicating the benzofuran-derived azadienes exhibit higher reactivities in

comparison with the benzofuran-derived oxadienes **2** (details were shown in Supporting Information). The structure of **5a** was determined by *X*-ray crystallography (see Supporting Information). Subsequently, the generality of this reaction was investigated by looking at various benzofuran-derived azadienes (Table 3). A wide range of monosubstituents on the benzofuran-derived azadienes **5** were well-tolerated in the reaction and **6b-6f, 6i-6j** bearing various substituents (*o*-Cl, *m*-OMe, *m*-Br, *p*-OMe, *p*-F, 5-Me, 5-Cl) were isolated in high to excellent yields (83%-99%). The reaction has also demonstrated compatibility with substrate uniting 2-thiophene moiety, which furnished the desired product with acceptable result (**6g**, 67% yield). Moreover, when *β*-naphthyl benzofuran-derived azadiene **5h** was utilized, the reaction furnished product **6h** in high yield (90 %). It is noteworthy that furan-derived azadiene **5k** was also effciently proceeded to afford the target product **6k** in 84% yield. In addition, acyclic oxadiene afforded ideal product in 9% yield. Encouragely, monocyclic oxadiene without dearomatization driving force was investigated, but no target product was observed. Moreover, several other *α,β*-unsaturated compounds were tested in our protocol and failed to furnish more spiro-BCHs (details were shown in Supporting Information).

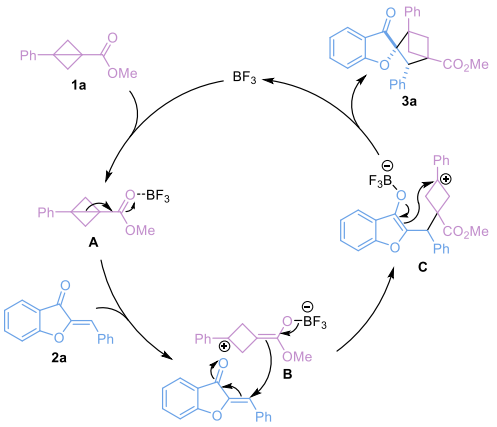
Scheme 3. Scale-up synthesis and synthetic transformations



To demonstrate the synthetic potential of the current protocol, scale-up synthesis and several transformations were performed as illustrated in Scheme 3. The [2π + 2σ] cycloaddition of BCB **1a** and benzofuran-derived oxadiene **2a** could be scaled up to 2.0 mmol scale almost without loss in efficiency, furnishing the desired product **3a** in 81% yield (Scheme 3a). Subsequently, several transformations of **3a** were conducted (Scheme 3b). The reaction of **3a** with MeMgBr produced the tertiary alcohol **7** in a high yield (83%). The carbonyl and ester group of **3a** was reduced to the hydroxyl group with DIBAL-H with high efficiency (**8**, 90% yield). Furthermore, Hydrolysis of ester group of **3a** afforded the carboxylic acid **9** in excellent yield (93%).

A plausible mechanism was proposed in Scheme 4 by utilizing the formation of **3a** as an example. Initially, the BCB **1a** coordinates to the BF_3 catalyst to afford species **A**, which undergoes enolization to intermediate **B.** The subsequent nucleophilic addition of **B** to the benzofuran-derived oxadiene **2a** (which might also be activated by coordination to the BF_3 catalyst) leads to the formation of carbocation species **C**. This key intermediate then undergoes intramolecular cyclization to form the desired adduct **3a** along with the regeneration of the BF_3 catalyst.

Scheme 4. Proposed catalytic cycle



In summary, we have developed a $BF_3{\cdot}Et_2O$-catalyzed formal [2π + 2σ] cycloaddition of benzofuran-derived oxa(aza)dienes with bicyclo[1.1.0]butanes. A series of diverse meaningful spiro[benzofuran-2,2'-bicyclo[2.1.1]hexanes] were obtained in an efficient (up to 99% yield) and economical way. The reaction proceeds under mild conditions with high functional group tolerance and broad substrate scope. We anticipate that the synthesized benzofuran-fused spirocycles can be instrumental in the discovery of pharmaceutical molecules and further studies of construction of spirocycles by dipolar cycloaddition of bicyclo[1.1.0]butanes are currently underway in our laboratory.

ASSOCIATED CONTENT

Supporting Information.
The Supporting Information is available free of charge at http://pubs.acs.org.
General information, experimental procedure, and spectroscopic data for all compounds (PDF)
X-ray crystallographic data of **3a** (CIF)
X-ray crystallographic data of **6a** (CIF)

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Note

The authors declare no competing financial interest.

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ABBREVIATIONS

BCHs, bicyclo[2.1.1]hexanes; 3D, three-dimensional; BCBs, bicyclo[1.1.0]butanes.

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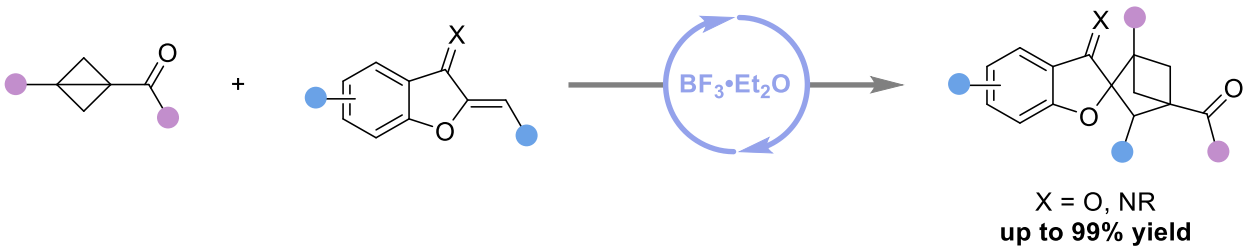

spiro-BCHs frameworks **formal [2π + 2σ] cycloaddition** **mild and metel-free conditions**

Rapid access of diverse spiro[benzofuran-2,2'-bicyclo[2.1.1]hexanes] via BF_3·Et_2O-catalyzed [2π + 2σ] cycloaddition of bicyclo[1.1.0]butanes with readily available benzofuran-derived oxa(aza)dienes.