Lewis Acid Catalysis Enables Switch from [2π+2σ] to Hetero-[4π+2σ] Cycloaddition Reactivity of Bicyclo[1.1.0]butanes for Spiro- and Bridged-Heterocycle Synthesis

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Dedicated to Professor Yong Tang on the occasion of his 60th birthday

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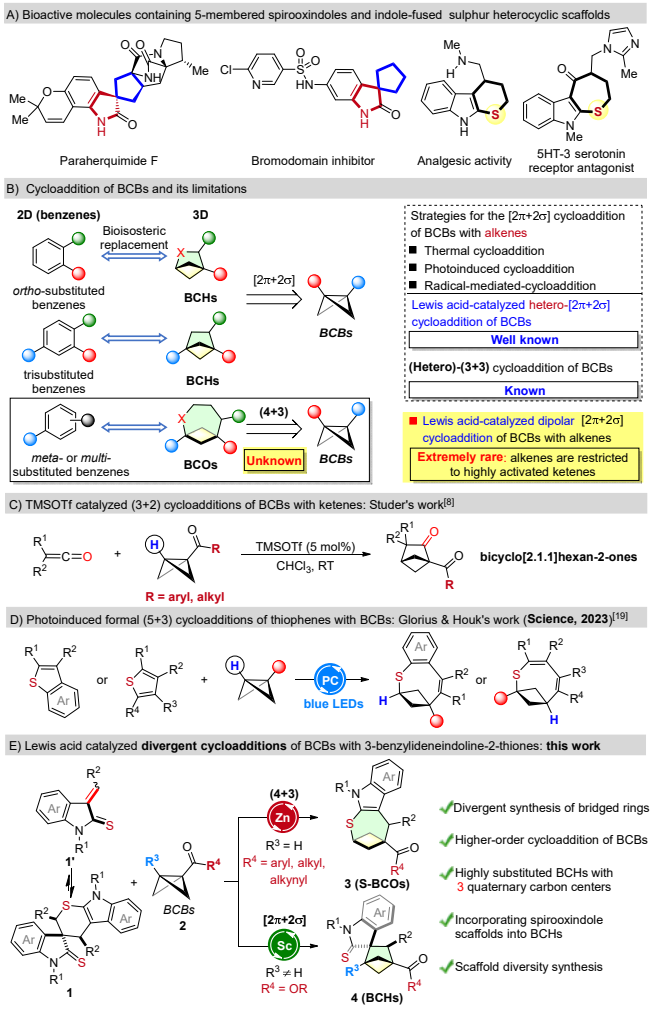
Abstract: The exploration of the complex chemical diversity of bicyclo[n.1.1]alkanes and their use as benzene bioisosteres has attracted considerable interest in the past 20 years. Regiodivergent syntheses of thiabicyclo[4.1.1]octanes (S-BCOs) and highly substituted bicyclo[2.1.1]hexanes (BCHs) through a Lewis acid-catalyzed formal cycloaddition of bicyclobutanes (BCBs) and 3-benzylideneindoline-2-thione derivatives are established. By using $Zn(OTf)_2$ as the catalyst, the first hetero-(4+3) cycloaddition of BCBs was achieved with broad substrate scope under mild reaction conditions. In contrast, the less electrophilic BCB ester undergo a $Sc(OTf)_3$-catalyzed formal [2π+2σ] reaction with 1,1,2-trisubstituted alkenes to generate BCHs featuring a spirocyclic quaternary carbon center. Furthermore, this innovative protocol has been proven to be useful in the efficient synthesis of an analogue of the lipid-lowering agent Lomitapide.

The diversity of scaffolds is a critical feature of compound library and greatly influences their success in biological screenings.[1] Therefore, developing a divergent strategy to synthesize molecules with privileged frameworks in drug discovery from a common building block holds great research significance. Spirocyclic compounds, particularly spirooxindoles,[2] are being increasingly utilized in drug discovery due to the conformational constraints imposed by a spiro-ring fusion, which often lead to improved physicochemical properties such as lipophilicity, solubility, and metabolic stability, compared to planar bioactive compounds (Scheme 1A).[3] Meanwhile, there has been a greater emphasis on the incorporation of $C(sp^3)$-rich bridged bicyclic scaffolds into chemical libraries for drug development, particularly considering the success of the “escape from flatland” concept in medicinal chemistry.[4] While significant advancements have been made in the divergent synthesis of spirocyclic frameworks, the catalytic divergent synthesis of bridged bicyclic scaffolds is still uncommon due to the absence of a versatile synthon for this purpose.[5]

Since their initial use as synthons in cycloaddition reactions to synthesize bicyclo[2.1.1]hexanes (BCHs), bicyclo[1.1.0]butanes (BCBs) have been increasingly employed as versatile building blocks for creating bridged bicyclo[n.1.1] frameworks.[6] Many kinds of 2π-components, including alkenes,[7] ketenes,[8] imines,[9] carbonyls,[10] (hetero)-arenes,[11] and triazolinediones,[12] have been used in the (hetero)[2π+2σ] reaction. Among them, the [2π+2σ] cycloadditions of BCBs with alkenes are particularly intriguing because the resulting cycloadducts (BCHs) can mimic both *ortho-, meta- and* multi-substituted benzenoids in drug design, depending on the BCH substitution pattern (Scheme 1B, left).[7h, 13]

In 1966, Blanchard has done seminal work on the thermally-driven intermolecular [2π+2σ] cycloadditions of BCBs and alkenes.[7a] Subsequently, de Meijere expanded the alkene scope to *α*-donor-substituted acrylonitriles.[7b] In 2006, the research group of Wipf conducted the first intramolecular [2π+2σ] cycloadditions of BCBs, resulting in an efficient pathway to ring-fused BCHs.[7c] In addition to these thermally induced reactions, the groundbreaking progress achieved by Glorius[7d] and Brown[7e] in the field of photocycloaddition of BCBs, has led to rapid advancements in radical [2π+2σ] cycloadditions between BCBs and alkenes over the past two years, yielding a diverse array of appealing BCHs.[7f,g] Besides the photocycloaddition strategy, Procter[7h] and Zheng[7i] independently developed elegant transition-metal-catalyzed radical [2π+2σ] cycloadditions of BCBs. But the use of alkenes is restricted to activated ones. Recently, Li[7j] and Wang[7k] expanded the range of alkenes to encompass activated and general alkenes by employing the innovative pyridine-boryl radical system.

Despite significant progress, the cycloaddition reactions of BCBs continue to encounter many obstacles (Scheme 1B). (1) The existing strategies for the cycloaddition of BCBs and alkenes are primarily restricted to radical processes and the range of substrates for alkenes is primarily restricted to terminal and cyclic



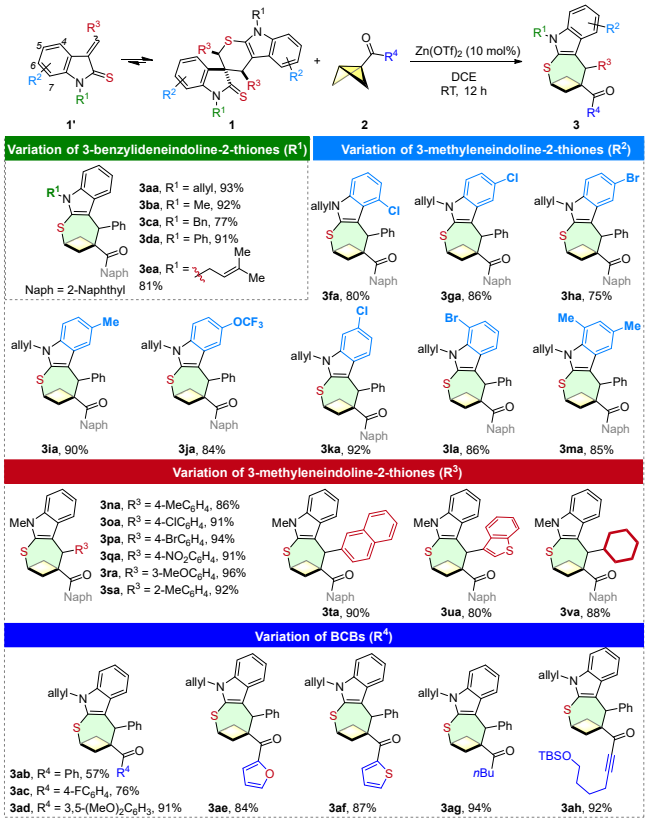
Scheme 1. Cycloadditions of BCBs and its scientific context

alkenes. Moreover, the approach for the cycloaddition of BCBs with highly hindered alkenes, such as 1,1,2-trisubstituted alkenes, is exceedingly uncommon.[7j,k] (2) While the Lewis acid-catalyzed hetero-(3+2) dipolar cycloadditions of BCBs, pioneered by Leitch's group,[9] have been well developed, the application of this strategy to the cycloaddition reactions of BCBs and olefins is not well explored; Studer reported the use of highly activated ketenes as the Lewis acid-catalyzed cycloaddition partner for synthesizing bicyclo[2.1.1]hexan-2-ones (Scheme 1C).[8] Therefore, it is highly desirable to develop a dipolar cycloaddition system that allows for the reaction between BCBs and 1,1,2-trisubstituted alkenes, thus increasing the scaffold diversity of valuable BCHs. (3) Besides BCHs and bicyclo[3.1.1]heptanes (BCHeps),[14] larger bridged bicyclic systems, such as bicyclo[4.1.1]octane frameworks (BCOs), are also utilized as substituted benzene mimetics, as reported by the Grygorenko group (Scheme 1B).[15] Moreover, BCO represents a valuable skeletal structure found in natural products.[16] However, atom-economical methods for synthesizing (hetero)BOC derivatives are extremely rare.[15,17] Therefore, developing formal (4+3) reactions of BCBs to construct (hetero)BOC scaffolds would greatly benefit their applications in medicinal chemistry. Of note, Deng[18a] and Glorius[18b] independently employed dipolar hetero-(3+3) cycloaddition of BCBs to synthesize hetero-BCHeps; Glorius and co-workers have successfully accomplished photoinduced formal hetero-(5+3) cycloadditions to synthesize unsaturated thiabicyclo[5.1.1]nonanes (Scheme 1D),[19] However, the hetero-(4+3) cycloaddition of BCB has not been achieved to date.

In order to address the aforementioned limitations, herein we present our endeavors towards the divergent synthesis of thiabicyclo[4.1.1]octanes (S-BCOs) and highly substituted BCHs featuring a spirocyclic quaternary carbon center. This is achieved by switching between (4+3)[20] and [2π+2σ] cycloaddition modes using different Lewis acid catalysts and BCBs (Scheme 1E).

Initially, we investigated the cycloadditions of the dimer (**1a**) of 3-benzylideneindoline-2-thione (**1a'**), which is formed through self-dimerization of **1a'** *via* a hetero Diels-Alder reaction,[21] with naphthyl ketone-substituted BCB **2a** in the presence of various Lewis acid catalysts. After many attempts, gratifyingly, with the use of $Zn(OTf)_2$, the formal (4+3) cycloaddition provided the desired S-BCO **3aa** featuring a valuable fused indole frameworks[22] in 96% NMR yield at room temperature (Scheme 2, condition A, see the ESI for details).

Using the optimized reaction conditions, we initially examined the substrate scope of the cycloaddition reaction involving various 3-methyleneindoline-2-thione derivatives. As shown in Scheme 2, this (4+3) protocol is amenable to a wide range of **1** with different types of *N*-substituents, including allyl (as in **3aa** and **3ea**),



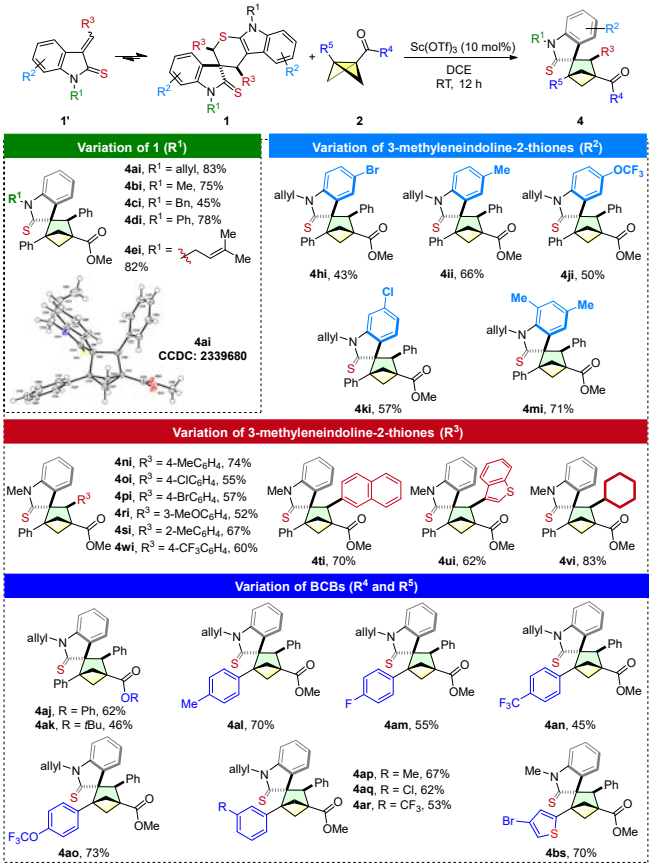
Scheme 2. Substrate scope investigation for (4+3) reactions.[a] [a] Condition A: the reactions were performed with **1** (0.1 mmol), **2** (0.1 mmol) and $Zn(OTf)_2$ (10 mol%) in 1,2-dichloroethane (DCE, 2.0 mL) at 25°C for 12 h; Isolated yields are shown.

alkyl (as in **3ba**),[23] benzyl (as in **3ca**) and aryl (as in **3da**) groups, and the products were obtained with good to excellent yields. The influence of the substituent at the phenyl moiety of **1** (R^2) on the reaction was then studied. The introduction of an electronically distinct substituent, such as chloro (**3fa**, **3ga** and **3ka**), bromo (**3ha** and **3la**), alkyl (**3ia** and **3ma**), and CF_3O (**3ja**), at positions C4, C5, C6, or C7 of substrate **1** was well-tolerated, resulting in high yields ranging from 75 to 92%. (**3fa-3ma**). Further exploration of the substrate scope was focused on 3-benzylideneindoline-2-thione derivatives bearing various substituents at the carbon-carbon double bond (R^3). Substrates **1**, which were substituted with both electron-donating groups (4-Me as in **3na**; 3-OMe as in **3ra**) and electron-withdrawing groups (4-halogen as in **3oa** and **3pa**; 4-NO_2 as in **3qa**), reacted smoothly under condition A; **1s** with an *ortho*-substituent actively engaged in the cycloaddition reaction, resulting in a 92% yield of product **3sa**. Besides substituted phenyl, 2-naphthyl (as in **3ta**) and 3-benzothienyl (as in **3ua**) were applicable. Notably, in addition to methyleneindoline-2-thiones with (hetero)aromatic substituents, the less reactive substrate **1v** containing an aliphatic substituent yielded S-BCO **3va** with an 88% yield.

Next, we turned our attention to the scope of BCB substrates (Scheme 2, bottom). The substituted phenyl (**2b-2d**), furanyl (**2e**), thiophenyl (**2f**) and alkyl (**2g**) substituted BCB ketones reacted efficiently with **1a** to give the corresponding S-BCOs in moderate to excellent yields (57–94%). It is worth noting that the functionalized alkynyl substituted Malins's BCB,[24] which has not been mentioned in previous cycloaddition reactions, exhibits selective formation of the desired cycloadduct **3ah** with a 92% yield.

During our investigation of 1,3-disubstituted BCB ester **2i** under conditions A, we discovered that when the less electrophilic BCB ester **2i** was used instead of BCB ketone, the expected (4+3) cycloadduct did not form. Instead, only methyl 3-phenylcyclobut-2-ene-1-carboxylate was observed with a 6% NMR yield. Unexpectedly, the reaction between **1a** and **2i**, using the reoptimized reaction conditions B (with 10 mol% $Sc(OTf)_3$ as the catalyst), resulted in the formation of the [2π+2σ] cycloadduct **4ai** instead of the corresponding formal [4π+2σ] product (see the ESI for details). The structure and relative stereochemistry of **4ai** were confirmed by X-ray crystallography analysis.[23]

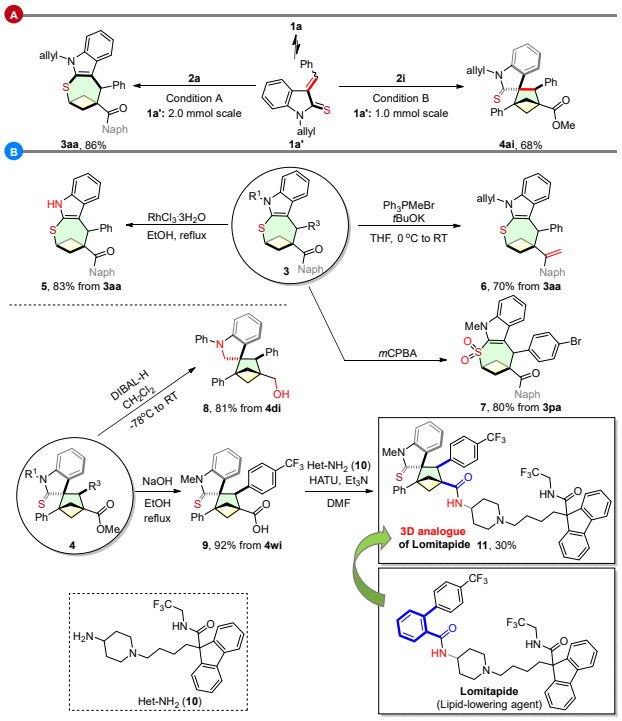
The scope and generality of this [2π+2σ] cloadditions in terms of 1,1,2-trisubstituted alkene substitution with 1,3-disubstituted BCB **2** is summarized in Scheme 3. In most cases, we observe the formation of cyclobutenes as by-products, resulting from the isomerization of bicyclobutane to cyclobutene.[9] The reaction led to the formation of the corresponding BCHs as a single diastereoisomer, and no (4+3) cycloadducts were observed. Firstly, the effect of *N*-substituents (R^1) of **1** on the reaction was investigated. The yield of the reaction was minimally influenced by the *N*-substituents (R^1) of substrate **1**. Replacement of *N*-allyl (**1a**) by *N*-benzyl group (**1c**) was a little exception as the yield decreased from 83% for **4ai** to 45% for **4ci**. This method is amenable to a series of 3-benzylideneindoline-2-thiones **1** bearing different R^2 substituents, including halogen (as in **4hi** and **4ki**), alkyl (as in **4ii** and **4mi**) and OCF_3 (as in **4ji**) groups at the C5–C7 positions of indoline-2-thione moieties, and led to the



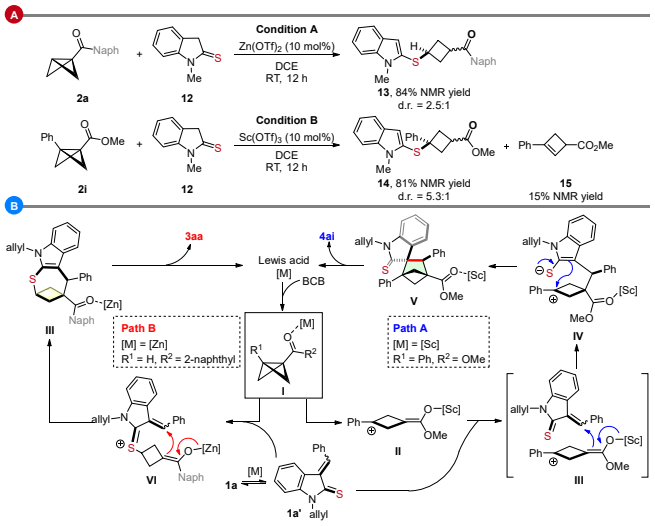
Scheme 3. Substrate scope investigation for [2π+2σ] reactions.[a] [a] Condition B: the reactions were performed with **1** (0.1 mmol), **2** (0.3 mmol) and $Sc(OTf)_3$ (10 mol%) in 1,2-dichloroethane (DCE, 2.0 mL) at 25°C for 12 h; Isolated yields are shown.

corresponding polysubstituted BCHs, which contained three quaternary carbon centers (including a spirocyclic quaternary carbon center), in reasonable yields (43-71%). As a trend, electron-donating groups R^2 generally led to higher yields (**4mi** *versus* **4ii** and **4hi**). Furthermore, the generality of the reaction condition for the substituents on the alkene moiety (R^3) of the substrates **1** was also investigated. A series of **1** are successful, including those with electron donating (as in **4ni**, **4ri** and **4si**) and withdrawing groups on aryl rings (as in **4oi**, **4pi** and **4wi**). In addition to the substituted phenyl and 2-naphthyl groups, a heteroaryl framework was also found to be applicable, as demonstrated by the 3-benzothienyl-substituted BCH **4ui**. Additionally, the cyclohexyl group was well tolerated, as shown by cycloadduct **4vi** (83% yield).

Subsequently, we examined a range of 1,3-disubstituted BCBs as cycloaddition partners for weakly reactive alkene **1a** (Scheme 3, bottom). These BCBs were found to be incompatible with Studer's [2π+2σ] reactions with highly activated ketenes.[8] This protocol is amenable to a variety of 1,3-disubstituted BCB esters, including methyl (**4ai**), phenyl (**4aj**) and *tert*-butyl (**4ak**) esters. The reaction of *para*- and *meta*-substituted phenyl bicyclo[1.1.0]butanes with different substituents on the aryl ring, including alkyl (as in **4al** and **4ap**), fluoro (as in **4am**), chloro (as in **4aq**), CF_3 (as in **4an** and **4ar**) and trifluoromethyloxy (as in **4ao**) which are popular in drugs and in agrochemicals, proceeded with



Scheme 4. Scale-up synthesis and synthetic transformations



Scheme 5. Mechanistic experiments and proposed mechanism

good efficiency. Of note, thienyl substituted BCB (**2s**) also reacted smoothly under condition B (70% yield).

The practicality of these divergent cycloadditions of BCBs was demonstrated by conducting a scale-up synthesis of **3aa** and **4ai** with almost maintaining yield (Scheme 4A). As shown in scheme 4B, the allyl group of indole **3aa** was readily removed in the presence of $RhCl_3$. The reaction of **3aa** with Wittig reagent afforded alkene **6** in 70% yield. The produced *S*-BCO **3pa** can easily be converted into biologically interesting sulfone (**7**) *via* oxidization with *m*-CPBA. Upon treating **4di** with DIBAL-H, both the thiolactam and the ester group were reduced to yield the desired spiroindoline **8**. Remarkably, we incorporated the highly substituted BCH unit with a spirocyclic scaffold into the structure of the lipid-lowering agent Lomitapide in just 2 steps from **4wi**, instead of the *ortho*-substituted phenyl ring. This highlights the practical synthetic utility of the resulting BCH scaffolds.

To gain insight into this transformation, indoline-2-thione **12**, which lacks an alkene moiety, was subjected to standard conditions A and B, resulting in the formation of the corresponding ring-opening products **13** and **14** (Scheme 5A). Although the exact mechanism remains unclear at present, we have proposed a plausible explanation for these divergent cycloadditions based on the above experiment and Leitch's seminal work.[9] The activation of BCB ester **2i** by Sc-Lewis acid potentially generates the enolate intermediate **II**. Then, C-C bond formation between the enolate and **1a'**, which is obtained by a reversible thia-Diels–Alder reaction from the dimer, affords the carbocation species **IV**. Ultimately, **IV** could undergo a ring-closing nucleophilic attack by activated thioenolate on the carbocation, resulting in the formation of the (3+2) cycloadduct **4ai** (Scheme 5B, path A). The mechanism involving a carbocation intermediate is consistent with the observed electronic effect sensitivity in BCB substrates. BCBs with electron-withdrawing groups (*e.g.*, *p*-and *m*-CF_3) on the phenyl group afford lower yield compared to substrates with electron-donating groups (**4al** *versus* **4an**; **4ap** *versus* **4ar**). Alternatively, when a more electrophilic and less hindered monosubstituted BCB ketone **2a** is used as a substrate, intermediate **VI** is selectively produced in the presence of a Zn catalyst and **1a'**. Finally, (4+3) product **3aa** is generated *via* the intramolecular Michael addition (path B).

In summary, a Lewis acid catalyzed divergent intermolecular cycloadditions of BCBs has been developed and enables the efficient synthesis of two types of bridged bicyclic rings, bicyclo[2.1.1]hexanes (BCHs) containing spirocyclic scaffolds and thiabicyclo[4.1.1]octanes (S-BCOs) from identical 3-benzylideneindoline-2-thione derivatives, respectively, through formal (3+2) and hetero-(4+3) cycloaddition. Use of readily available starting materials, mild reaction conditions, high yields, as well as versatile functionalization of the cycloadducts make this approach very practical and attractive. Notably, this is the first report on the (4+3) cycloadditions of BCBs to synthesize uncommon BCO derivatives. Additionally, the current formal (3+2) reactions represent rare examples of BCBs with highly hindered 1,1,2-trisubstituted alkenes. Considering the newfound reactivity of this cycloaddition and the significant need for BCH and BOC scaffolds as bioisosteres, we anticipate that this approach will yield positive outcomes in both synthetic and medicinal chemistry.

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Keywords: Bicyclic compounds • Cycloaddition • Spirooxindoles • Strained molecules • Heterocycles

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[23] Deposition numbers 2339679 (for **3ba**) and 2339680 (for **4ai**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

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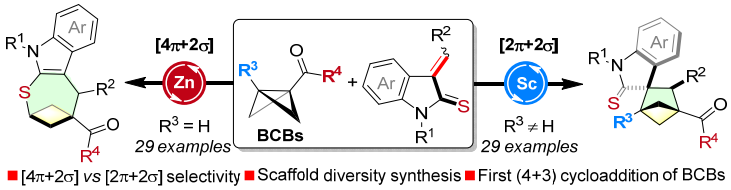
Entry for the Table of Contents



Regiodivergent syntheses of thiabicyclo[4.1.1]octanes (S-BCOs) and highly substituted bicyclo[2.1.1]hexanes have been achieved through a Lewis acid-catalyzed cycloaddition of bicyclobutanes (BCBs) and 3-benzylideneindoline-2-thione derivatives. Moreover, rapid access of S-BCOs, which were not readily accessible by known methods, has been realized through $Zn(OTf)_2$-catalyzed uncommon [4π+2σ] cycloadditions of BCBs.