Lewis Acid Catalyzed (4π+2σ) Annulation of Bicyclobutanes with Dienol Ethers for the Synthesis of Bicyclo[4.1.1]octanes

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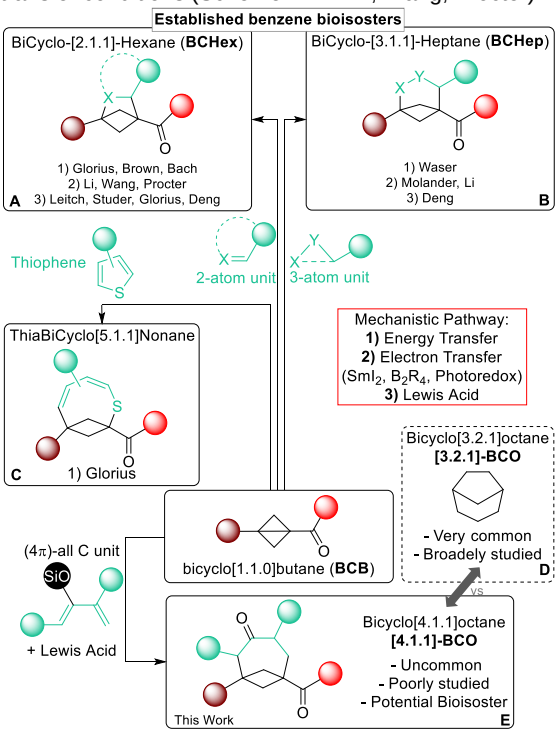
Abstract: Bicyclic carbocycles containing a high fraction of Csp^3 have become highly attractive synthetic targets because of the multiple applications they have found in medicinal chemistry. The formal cycloaddition of bicyclobutanes (BCB) has recently been extensively explored for the construction of both bicyclohexanes and bicycloheptanes. Adopting this approach for the synthesis of medium-sized bridged carbocycles has instead remained more limited. We report herein the formal (4π+2σ) cycloaddition of BCB ketones with silyl dienol ethers. The reaction occurred in the presence of aluminium triflate as a Lewis acid catalyst. Upon acidic hydrolysis of the enol ether intermediates, rigid bicyclo[4.1.1]octanes (BCOs) diketones could be easily accessed in good to very good yields. This convenient and scalable procedure was tolerant towards a range of both aromatic and aliphatic substituents on both the BCB substrates and the dienes. The obtained BCO products could be smoothly functionalized through reduction and cross-coupling reactions.

Saturated polycyclic carbocycles have gained growing attention in both medicinal and organic chemistry.[1] Molecules that incorporate these motifs exhibit enhanced pharmacokinetic and physiochemical properties compared to more common Csp^2-rich bioactive synthetic compounds, and have become privileged candidates for drug-discovery.[2] The increased conformational rigidity that is characteristic of these topologically more intricate polycyclic frameworks is especially important as it can lead to improved affinity to their biological targets, as demonstrated also in many bioactive natural products.[3] These considerations explain why the efficient construction of bicycloalkanes as core elements of more complex systems has become a primary goal for synthetic chemists, which – however – demands addressing the challenges coming from their inherent complexity.[4] In particular in the few years, the use of carbonyl-substituted bicyclo[1.1.0]butanes (BCBs) in strain-releasing annulation reactions has emerged as a convenient modular approach for the generation of bicyclic carbocycles and their heterocyclic analogs.[5] The synthesis of bicyclo[2.1.1]hexanes (BCHex's) through the formal (2π+2σ) cycloaddition of BCBs has been extensively studied to access new bioisosteres of the benzene ring.[1c] Following on to the seminal reports by the groups of Glorius and Brown, several methods have appeared that rely on radical pathways, either under light induced energy transfer (Scheme 1.A.1: Glorius, Brown, Bach) or electron-transfer conditions (Scheme 1.A.2: Li, Wang, Procter).[6]



Scheme 1. Formal cycloadditions of BCB carbonyl derivatives for: A) the synthesis of Bicyclohexanes; B) the synthesis of Bicycloheptanes; C) the synthesis of Thiabicyclononanes; D) Very common Bicyclo-[3.2.1]-octane scaffold; E) the synthesis of all-carbon Bicyclo-[4.1.1]-octanes ([4.1.1]-BCO, this work).

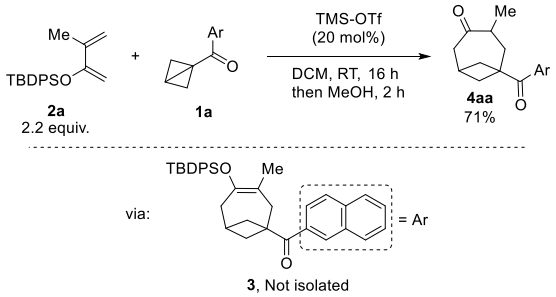
Lewis acid catalysis has also proven effective to promote annulations following a polar mechanism (Scheme 1.A.3: Leitch, Studer, Glorius, Deng).[7] As a

recent expansion, the annulation of BCBs with three-atom partners has been used to obtain bicyclo[3.1.1]heptanes using the same three activation modes (BCHeps) (Scheme 1.B: Molander, Waser, Li, Deng).[8] Cycloadditions of BCB affording larger saturated bicycloalkanes have however remained unexplored so far, and only one example exists, in which this kind of transformation is employed to form unsaturated thiabicyclo[5.1.1]nonanes (Scheme 1.C; Glorius).[9]

Medium sized carbocycles and their bridged variants are abundant among both natural and pharmacologically relevant compounds.[10] For example, bicyclo[3.2.1]octane ([3.2.1]-BCO) – a higher homolog of BCHex's and BCHep, as well as a conformationally rigid analog of cycloheptane – can be found in thousands of bioactive terpenoid derivatives, and extensive research has focused on the synthesis of this scaffold (Scheme 1D).[11] Bicyclo[4.1.1]octane (BCO) is rarer in nature,[12] it has been much less studied, and only very few preparative methods have been so far established that are limited in scope and lack convergence.[13] The still undisclosed value of BCO has been however highlighted in a recent study conducted by the group of Grygorenko showcasing the improved lipophilicity of this unique motif and its potential function as an isosteric replacement for both aromatic and saturated monocyclic carbocycles, with the additional advantages offered by its conformational rigidity.[13c] Furher investigations on BCO ring systems would be of great benefit in the perspective of their applications in medicinal chemistry. Nonetheless, progressing in this direction is hampered by the lack of efficient synthetic methods granting an expedient access to these scaffolds.

The annulation of BCBs with four-carbon partners such as dienes appears as an attractive convergent strategy to access BCOs. However, dienes can also act as two-carbon partners, leading to the competitive formation of BCHexs. This is especially true when the annulation proceeds via radical intermediates. For instance, the previously reported utilization of weakly or non-polarized dienes under photochemical conditions in annulations with BCBs only resulted in the formation of the (2π+2σ) BCHex products,[14] while the only reported transformation giving access to medium-sized bicyclic scaffolds relied on a photo-induced dearomative expansion of thiophenes.[9] We therefore wondered if Lewis acid catalysis might constitute a more viable alternative. We envisaged that a suitable BCB carbonyl derivative upon activation by a Lewis acid would promptly react with a polarized diene and generate a reactive Michael acceptor intermediate, on which favoring 1,4- rather than 1,2- addition would be easier to achieve. Herein, we describe the synthesis of BCO through the formal (4π+2σ) cycloaddition of BCB ketones with dienol silyl ethers under Lewis acid catalysis through the successful implementation of this strategy (Scheme 1.E). To the best of our knowledge, this is the first application of BCBs to the generation of medium-sized bridge substituted all-carbon carbocycles.

To assess the validity of our hypothesis, we became inspired by the work of Studer and co-workers about the formal cycloaddition of BCB ketones with ketenes using TMS-OTf as the catalyst.[7b] At the start of our studies, this was the only report describing the formation of two C-C bonds across the BCB framework under Lewis acid catalysis (for studies published during our investigations, see ref. 7d,e). More stable naphthoyl BCB **1a** was selected as our model substrate and treated with an excess (2.2 mmol) of *tert*-butyl diphenylsilyl (TBDPS) dienol ether **2a** in DCM and in the presence of TMS-OTf (20 mol%) at room temperature. A check of the reaction after 16 hours showed the full conversion of our starting material and the formation of a less polar compound (later identified as silyl enol ether **3**). After methanol was added and the resulting mixture was stirred for 2 hours, we observed that **3** had completed transformed into BCO ketone product **4aa**, which could be isolated in 71% yield.

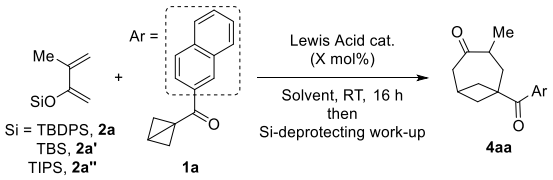


Scheme 2. Discovery of the formal (4π+2σ) cycloaddition of BCB ketone **1a** with dienol silyl ether **2a** to give BCO diketone **4aa** through intermediate enol **3**.

Because the purification of the intermediate silyl enol ether was challenging, we focus directly in optimizing the formation of ketone **4aa**.[15] As the complete conversion of **3** to **4aa** through the sole addition of MeOH was difficult to achieve, an excess of TMS-OTf was used during the hydrolytic work-up of the reaction mixture. When trying to further improve the outcome of the transformation (Table 1), a screening of silyl protecting groups on the dienol ether using 20 mol% of TMS-OTf as catalyst showed that, compared to TBDPS (entry 1) the smaller and less stable TBS (entry 2) and TIPS (entry 3) provided **4aa** in lower yield. $Ga(OTf)_3$ – the catalyst of choice in the annulation of BCB ketones with imines published by the group of Leitch[7a] – led to an increased yield of over 80% (entry 4). Other Lewis acids furnished inferior results (see ESI, for details). Reducing the catalytic loading to 10 mol% did not affect the efficiency of the reaction (entry 5). On the contrary, a smaller amount of the dienol ether (1.2 instead of 2.2 equivalents) afforded a significantly diminished yield (entry 6). $Al(OTf)_3$ was next investigated as a more sustainable alternative to $Ga(OTf)_3$. No diminution of yield occurred when the reaction was performed using

10 mol% $Al(OTf)_3$ (entry 7). A brief evaluation of other solvents confirmed the superiority of DCM to other chlorinated (entry 8) and especially non-chlorinated ones (entry 9).[18] In addition, further lowering the catalytic loading of $Al(OTf)_3$ to 5 mol% provided the product in even higher 90% yield (entry 10); this was not the case with $Ga(OTf)_3$ (see ESI).

Table 1. Optimization of the formal (4π+2σ) cycloaddition of BCB ketone **1a** with dienol silyl ether **2a**.[a]



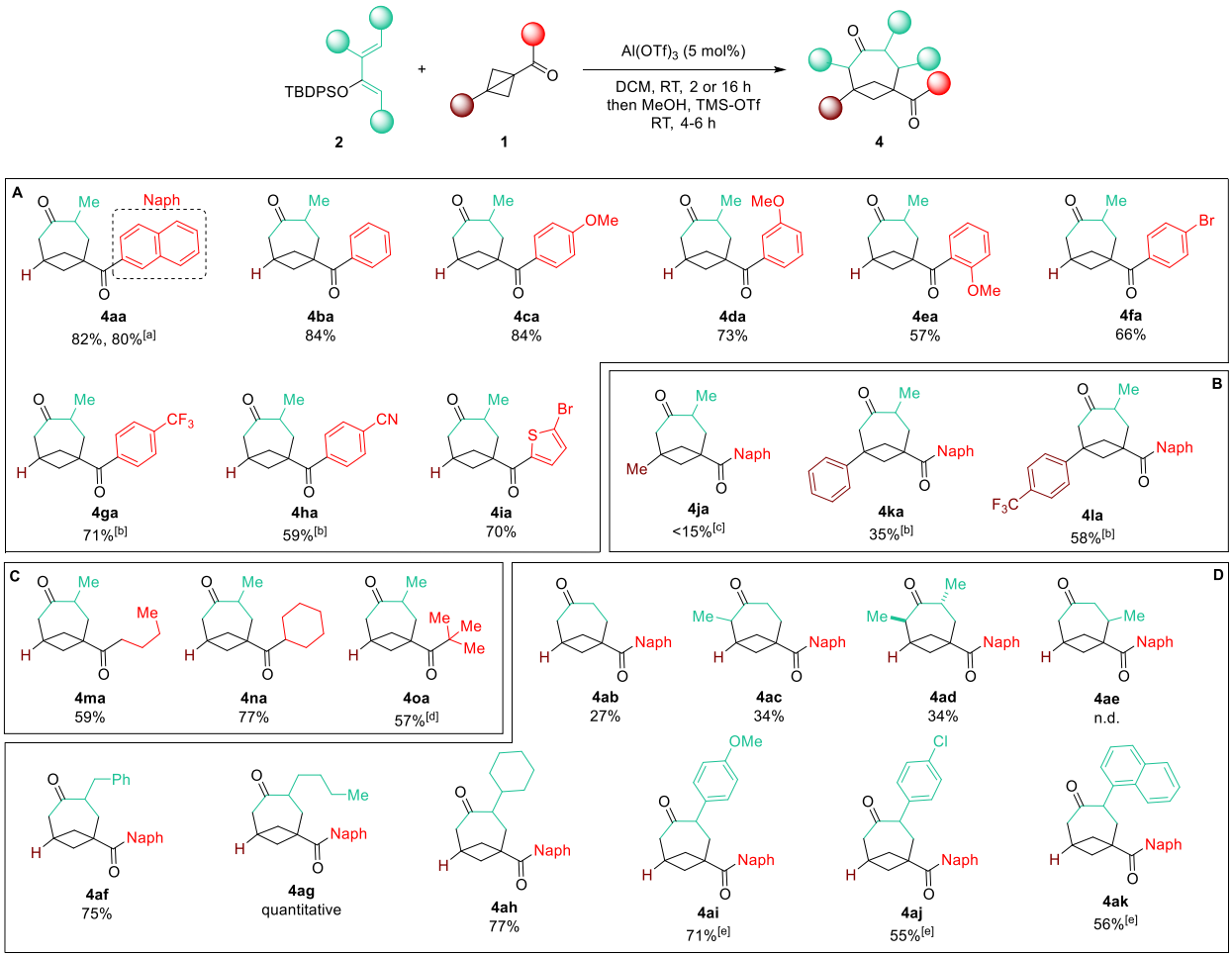
Entry[l]	Si group	Lewis acid (X mol%)[l]	Solvent	Yield[a]
1	TBDPS	TMS-OTf (20)	DCM	70%
2	TBS	TMS-OTf (20)	DCM	33%
3	TIPS	TMS-OTf (20)	DCM	52%
4	TBDPS	$Ga(OTf)_3$ (20)	DCM	83%
5	TBDPS	$Ga(OTf)_3$ (10)	DCM	81%
6[b]	TBDPS	$Ga(OTf)_3$ (10)	DCM	61%
7	TBDPS	$Al(OTf)_3$ (10)	DCM	84%
8	TBDPS	$Al(OTf)_3$ (10)	$CHCl_3$	75%
9	TBDPS	$Al(OTf)_3$ (10)	Et_2O	57%
10	TBDPS	$Al(OTf)_3$ (5)	DCM	90%
11[c][d]	TBDPS	$Al(OTf)_3$ (5)	DCM	74%
12[c][e]	TBDPS	$Al(OTf)_3$ (5)	DCM	82%
13[c][f]	TBDPS	$Al(OTf)_3$ (5)	DCM	78%

Reaction conditions: 0.15 mmol BCB ketone **1a** (1.0 equiv), 0.33 mmol silyl dienol ether **2a-a''** (2.2 equiv.), Lewis acid (X mol%), in 1.5 mL solvent (0.1 M) at RT, overnight; Quench: 1.5 mL MeOH, 0.10 mL TMS-OTf (6.0 mmol, 4.0 equiv.), at RT, 4 hours. [a] Isolated yield upon column chromatography. [b] with 0.36 mmol **2a** (1.2 equiv.). [c] 0.30 mmol BCB ketone **1a** (1.0 equiv), 0.66 mmol silyl dienol ether **2a** (2.2 equiv.), Lewis acid (X mol%), in 3.0 mL solvent (0.1 M), at RT, 2 hours. [d] Upon removal of DCM: 0.75 mL TBAF (1.0 M in THF, 2.5 equiv.) in 3.0 mL THF, 0 °C to RT, 4 hours. [e] Quench: addition of 3.0 mL MeOH, 0.20 mL TMS-OTf (12 mmol, 4.0 equiv.), at RT, 4 hours. [f] Quench: addition of 2.6 mL MeOH, 0.40 mL HCl (3.0 M in MeOH, 4.0 equiv.), at RT, 2 hours.

Finally, an adjustment of the whole procedure was undertaken, with a specific focus on the silyl-deprotecting work-up after the formal cycloaddition step. For ensuring reproducibility, the scale of the process was doubled to 0.30 mmol related to ketone **1a**. The same scale was later maintained during the investigation of the scope. Treatement with TBAF upon solvent-switch to THF gave inferior results (entry 11) compared to the protocol involving the addition of TMS-OTf and MeOH (entry 12), which was therefore adopted as our optimal procedure. Changing TMS-OTf to a solution of HCl in methanol provided **4aa** in a comparable yield (entry 13), and can be thus considered as a more cost-effective alternative to our standard method.

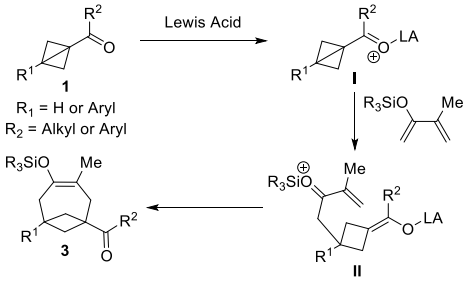
With an optimized protocol in hands, we moved to assess the generality of our method (Scheme 3). We started by considering variations of the BCB ketone substrates, submitting them to the reaction protocol in the presence of model diene **2a**. Aryl-substituted BCB ketones were initially studied (Scheme 3A). A further five-fold scale-up of the reaction to 1.5 mmol of **2a** produced **4aa** in 80% yield, demonstrating the excellent reproducibility of the procedure. Moving from naphthoyl BCB **1a** to phenyl ketone **1b**, afforded BCO **4ba** in 84% yield. The presence of an electron-donating methoxy substituent on the aromatic ring was also tolerated very well in both the *para* (**4ca**, 84% yield) and the *meta* (**4da**, 73% yield) positions. When the OMe group was instead in *ortho* position, BCO **4ea** could be isolated in 57% yield. Electron-withdrawing substituents were also compatible and similar yields were obtained as with more electron-rich starting materials, albeit longer reaction times were necessary. Specifically, substrates having a bromine atom, a trifluoromethyl, or a nitrile in the *para* position of the aryl group gave BCO derivatives **4g-ia** with yields in the 60-70% range. Thiophene-containing BCB **1i** was also a competent substrate, which could be converted into the corresponding product **4ia** in 70% yield. At this point, we became curious about how BCBs with substituents on the bridgehead of the bicycle performed (Scheme 3B). A methyl in such a position was poorly tolerated: product **4ja** was in fact collected in less than 15% yield. With aryl groups, the transformation worked better. **1k**, which contained an unsubstituted phenyl ring at the bridgehead carbon, was converted into **4ka** in 35% yield. In the presence of a more electron-poor trifluoromethyl phenyl group, the expected cyclization product **4la** was generated in 58% yield. Finally, alkyl BCB ketones were also good starting materials (Scheme 3C): a primary ^{n}butyl, a secondary and cyclic cyclohexyl, and a tertiary ^{t}butyl groups on the carbonyl of the substrate were all tolerated, furnishing aliphatic BCO **4ma**, **4na** and **4oa** in 59%, 77% and 57% yields, respectively. Noteworthy, X-ray diffraction of the latter compound enabled us to get a confirmation of the caged bicyclic framework of the synthesized BCO derivative.[19]

We then turned our interest towards varying the TBDPS dienol ether in the reaction with model naphthoyl BCB **1a** (Scheme 3D). The substitution pattern on this 4π component impacted significantly the outcome of the reaction. Indeed, unsubstituted **2b** and 1-methyl substituted **2c** both gave corresponding BCO derivative, **4ab** and **4ac**, in modest yields (27% and 34%). Diene **2d** – which contained methyl groups in C1 as well as in C3 – also gave a moderated yield but – interestingly – product **4ad** was formed as a single *trans* diastereoisomer, as determined by X-Ray diffraction.[20] No annulation was instead observed when **XXe**, bearing a methyl group on C4, was used, and only a complex mixture formed in this case. When we turned back our attention to dienol ethers with one substituent at C3 position, we found that the reaction worked consistently well with different substituents. Alkyl groups were all tolerated: benzyl-containing BCO **4af** was synthesized in high 75% yield, whereas **4ag** and **4ah** – with a ^{n}butyl and a cyclohexyl groups – were delivered quantitatively and in 77% yield. With aryl C3-substituted dienes, a readjustment of the procedure was necessary: a slight decrease of the amount of the dienol ether to 2.0 equivalents was possible, but a longer reaction time was needed, as well as a larger excess of TMS-OTf during the silyl-deprotecting work-up. The lower reactivity of these compounds and the higher stability of the silyl enol ether reasonably account for these changes. The annulation was more effective with diene **2i** bearing an electron-rich *p*-anisyl group in C3, delivering **4ai** in 71% yield. With the less electron-donating aryl substituents *p*-chorophenyl and 1-naphthyl, BCO **4aj** and **4ak** were accessed in 55% and 56% yields.



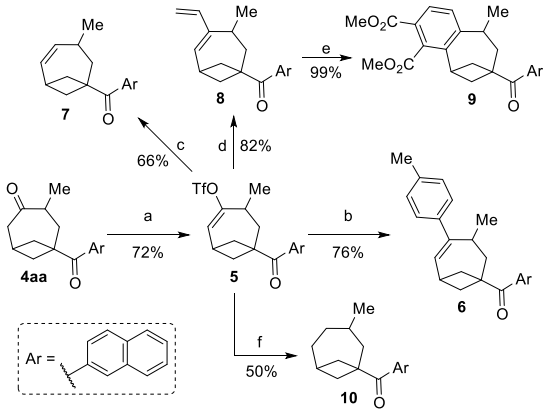
Scheme 3. Scope of the reaction. **A**: Products obtained from diverse aryl BCB ketones **1a-i**. **B**: Products obtained from BCB ketones bearing a substituent at the bridgehead positions **1j-l**. **C**: Products obtained from diverse alkyl BCB ketones **1m-o**. **D**: Products obtained from diversely substituted TBDPS dienol ethers **2a-k**. General conditions: 0.30 mmol (1.0 equiv.) BCB Ketone **1**, 0.66 mmol (2.2 equiv.) TBDPS dienol ether **2**, 5 mol% $Al(OTf)_3$, 3.0 mLDCM (0.1 M), RT, 2 hours; then: 3.0 mL MeOH, 12 mmol TMS-OTf (4.0 equiv.), RT, 4-6 hours. [a] Performed on 1.5 mmol scale. [b] The reaction was run overnight. [c] Purity < 90%. [d] Average yield over two reiterations. [e] With 0.60 mmol (2.0 equiv.) TBDPS dienol ether **2**, overnight; for the quench 1.2 mmol TMS-OTf (8.0 equiv.) were used.

We did not perform any in-depth mechanistic study. Nonetheless, analogies with previous reports describing the formal cycloadditions of BCB ketones with polarized reacting partners under Lewis acid catalysis make plausible that the activated substrate **I** would undergo nucleophilic attack of the enol moiety of the diene at the bridgehead position (Scheme 4).[5f] After this initial C-C bond-forging step, the resulting enolate intermediate **II** would cyclize by attacking the enone-like fragment. The pronounced sensitivity of the outcome of the process to substitution at the bridgehead C-atom seem to be in agreement with this speculation. The shielding effect of the bulky silyl group on the oxygen may be at the origin of the exclusive 1,4-addition selectivity.



Scheme 4. Plausible mechanism of the formal (4π+2σ) cycloaddition of BCB ketones **1** with dienol silyl ether **2**.

In order to evaluate the synthetic versatility and utility of the obtained BCO diketones, their modifications was then investigated (Scheme 5). We specifically focused on BCO **4aa**, containing a naphthyl group on the carbonyl function. In this case, chemoselective functionalization is facilitated as only the carbonyl group on the bicyclooctane scaffold is enolizable. Accordingly, **4aa** could be smoothly converted into enol triflate **5** in 72% yield under kinetic-controlled conditions.[21] The latter compound was the starting material for a series of subsequent transformations. Styrene **6** and alkene **7** were both accessed in good yields through a Suzuki cross coupling reaction[22] and a Pd0-catalyzed reduction with Bu_3SnH,[23] respectively. A Stille coupling was employed to synthesize diene **8**,[24] which was subsequently refluxed with DMAD followed by oxidation with DDQ to forge product **9** quantitatively, in which the BCO bicycle is condensed with an aromatic ring. Finally, the completely reduced, saturated skeleton of bicycle[4.1.1]octane could be accessed by catalytic hydrogenation of **10** in the presence on Li_2CO_3.[25] Unfortunately, a yield higher than 50% could be obtained because of its sensitivity to overreduction.



Scheme 5. Modifications of BCO product **4aa**. Reaction conditions: a) KHMDS, $PhNTf_2$, THF, -78 °C. b) $Pd(dppf)Cl_2$ (6 mol%), K_3PO_4, p-TolB$(OH)_2$, THF, 65 °C. c) $Pd(PPh_3)_4$ (2 mol%), LiCl, Bu_3SnH, THF, RT. d) $Pd(PPh_3)_4$ (2.5 mol%), LiCl, $Bu_3SnCH{=}CH_2$, THF, 65 °C. e) DMAD, $PhCH_3$ 120 °C then DDQ, 120 °C. f) H_2 (1 atm), Pd/C (5 mol%), Li_2CO_3, EtOAc, RT.

In summary, the first formal (4π+2σ) cycloaddition of BCB ketones with dienol silyl ethers has been disclosed. The reaction occurs under mild conditions, using easily available $Al(OTf)_3$ as a Lews acid catalyst, and represents a convenient modular method for the synthesis of uncommon biyclo[4.1.1]octane carbocycles. The latter could be generally obtained in good to very good yields, with a wide tolerance of substituents on both the substrate and the diene, including alkyl as well as electron-rich and –poor aryl groups. The obtained products were available for an array of further transformations, giving access to BCO derivatives with different fractions of Csp^3. As the importance of biyclo[4.1.1]octanes starts emerging in the search for new bridged cycloalkanes with bioisosteric properties, we do believe that our protocol for the expedient preparation of these intriguing frameworks will contribute to facilitate and accelerate research on them.

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Keywords: Bicyclobutanes • Bicyclooctanes • Dienol silyl ethers • Annulation reactions • Lewis acid catalysis

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[20] Deposition Number for **4ad**: 2333992; contains 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 www.ccdc.cam.ac.uk/structures.

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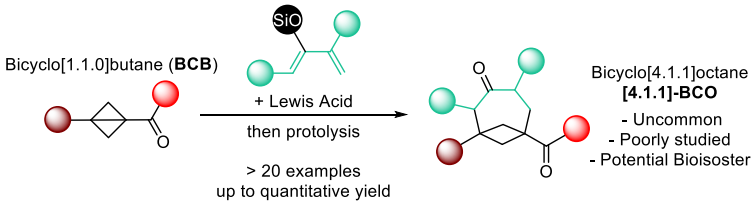

With $Al(OTf)_3$ as a Lewis acid catalyst, aryl and alkyl bicyclobutane ketones were reacted with dienol silyl ethers in a formal (4π+2σ) cycloaddition providing bicyclo[4.1.1]octanes (BCOs). More than twenty diketone derivatives were obtained in good to very good yields using 5 mol% Lewis acid at room temperature for annulation followed by a protolytic work-up.