Silver-Catalyzed Dearomative [2π+2σ] Cycloadditions of Indoles with Bicyclobutanes: Expedient Access to Indoline Fused Bicyclo[2.1.1]hexanes

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Supporting Information Placeholder

ABSTRACT: Bicyclo[2.1.1]hexanes (BCHs) are becoming ever more important in drug design and development as bridged scaffolds that provide underexplored chemical space, but are difficult to access. Here a novel silver-catalyzed dearomative [2π+2σ] cycloaddition strategy for the synthesis of indoline fused BCHs from *N*-unprotected indoles and bicyclobutane precursors is described. This strain-release dearomative cycloaddition operates under mild conditions, tolerates a wide range of functional groups and is capable of forming BCHs bearing three quaternary carbon centers with up to 99% yield, a longstanding challenge in the field. In addition, a scale-up experiment and the synthetic transformations of the cycloadducts further highlighted the synthetic utility.

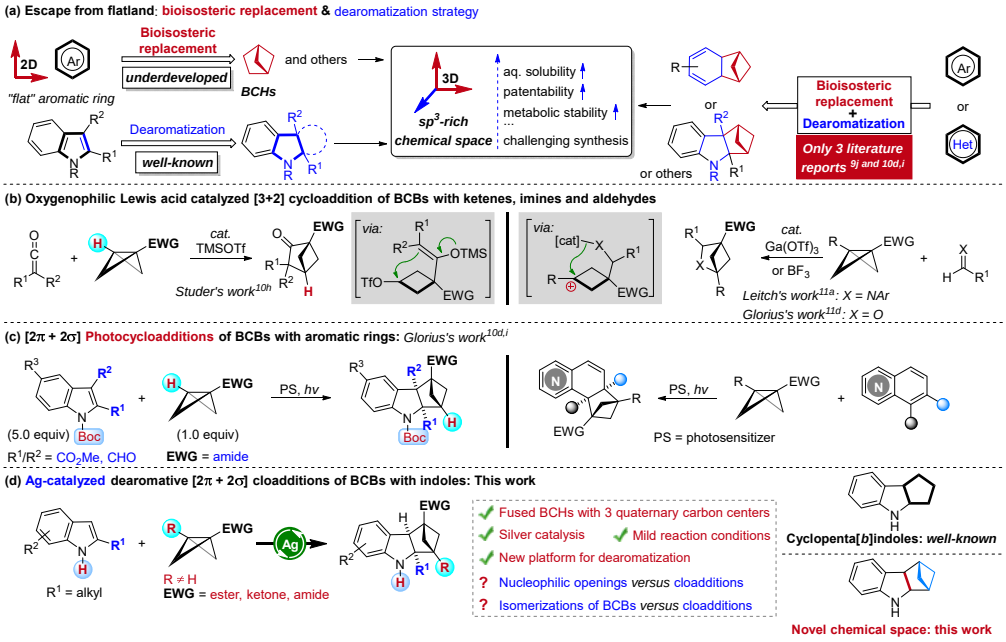
To improve the odds of drug development success through chemical synthesis, a new trend has emerged to increase the fraction of sp^3 (Fsp^3)-hybridized carbons of potential drug candidates (so-called Escape-from-Flatland concept).[1] To realize this concept, both the bioisosteric substitution of aromatic ring with a saturated analogue[2] and dearomatisation strategy,[3] based on decades of scientific research, proved to be effective (Scheme 1a, left).

In this context, the preparation of bridged bicyclic molecules as benzene bioisosteres has flourished. For example, bicyclo[1.1.1]-pentane (BCP)[4,5] and bicyclo[3.1.1]heptane (BCHep)[6] derivatives have been successfully employed as *para*- and *meta*-substituted benzene mimetics, respectively. Besides these, substituted bicyclo[2.1.1]hexanes (BCHs) are emerging three-dimensional (3D) bioisosteres for *ortho*- and *meta*-substituted benzenes.[2b,7] Consequently, considerable effort has been devoted to the development of efficient methods for the synthesis of these rigid bridge rings.[7-11] Among those methods for synthesizing BCHs, the most common and well-known process is intramolecular crossed [2+2] cycloaddition of 1,5-dienes.[8b-e] Alternatively, the intermolecular [2π+2σ] cycloaddition of 2π-components and bicyclo[1.1.0]butanes (BCBs)[9] is also an efficient method for making BCHs[7b,10] and hetero-BCHs.[11] In 1966, Blanchard has done pioneering works on the intermolecular BCB-alkene cycloadditions enabled by cleavage of the strained central C–C bond of BCB *via* thermolysis.[10a] More recently, in 2006 Wipf has described the merit of intramolecular thermal conversions of BCBs with alkenes for the synthesis of complex tricyclic compounds.[10c] Apart from thermally induced cycloadditions of BCBs, the applicability of these [2π+2σ] cycloadditions has been greatly expanded in the past two years with the use of other novel strategies, including Glorius[10d] and Brown's[10e] photocycloaddition protocols enabled by triplet energy transfer, Procter's[7b] SmI_2-catalysed redox reaction, and Li[10f] and Wang's[10g] pyridine-boryl radical catalysis. Moreover, oxygenophilic Lewis acid catalyzed [3+2] reactions of BCBs with ketenes, imines and aldehydes are reported by Studer,[10h] Leitch,[11a] and Glorius[11d] respectively (Scheme 1b). Despite the significant advances made in this area for the synthesis of BCH derivatives, such intermolecular cycloadditions of BCBs have been mainly restricted to general alkenes and electron-deficient two-atom components. The corresponding reactions with electron-rich two-atom components are relatively rare.[10e,f] Therefore, discovery of new catalytic system for the cycloadditions of BCBs with electron-rich 2C synthons for further enrichment of the structural diversity of the valuable BCH products are still highly desirable.

Indole and indoline derivatives are ubiquitous structural motifs found in an array of bioactive natural compounds (*e.g.,* MK-0524, paspaline, polyveoline and other cyclopenta[*b*]indole/indoline alkaloids).[12] Moveover, the 2D aromatic heterocycle indole represents a privileged structure of numerous synthetic drug molecules. Recently, dearomative transformation of indoles, such as the dearomative 1,3-dipolar cycloadditions,[13] gained more and more research interest. Because it offers new possibilities to go from 2D aromatic rings to more architecturally more complex 3D structures.

Along these lines and on the basis of our experience in strained rings chemistry,[14] we envisioned that the combination of cycloadditions of BCBs with dearomatisation strategy would further expand sp^3-rich chemical space for drug discovery (Scheme 1a, right). Herein we report a silver catalyzed dearomative [2π+2σ] cycloadditions of indoles with bicyclobutanes that forms fused BCHs (Scheme 1d). Several points are noteworthy: (1) the reaction yields fused BCHs with three quaternary carbon centers under mild reaction conditions. These structures would otherwise be difficult to access; (2) despite the fact that the [2π+2σ] cycloadditions of BCBs with alkenes have been disclosed, the dearomative variants are rarely investigated,[9j and 10d,i] due to severe challenges associated with breaking the increased stabilization conferred by aromaticity. As a rare example, Glorius and co-workers reported an elegant photochemical [2π+2σ]-cycloadditions of indoles with monosubstituted BCBs in the last year. However, the substrate scope was limited to *N*-protected indoles bearing an electron-withdrawing group at the C2 or C3 position (Scheme 1c);[10d] (3) BCBs easily undergo silver catalyzed rearrangements to corresponding dienes by cleavage of the C–C edge bonds in BCBs.

Scheme 1. Dearomative [2π+2σ] Cyloadditions of BCBs and its scientific context

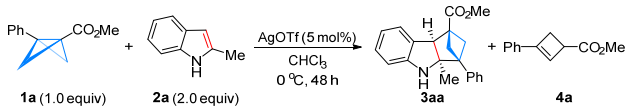


By contrast, direct activation of the central bond of BCBs by carbophilic silver catalysis is still scarce;[15] (4) Besides these, the other problem that needs to be solved is how to suppress the side reactions including the competitive bicyclobutane-to-cyclobutene isomerization[11a] and the ring opening of BCBs.[16]

Optimization studies began with the cycloaddition of 1,3-disubstituted BCB ester **1a** with 2-methyl-1*H*-indole **2a**. Upon screening a series of reaction parameters, the desired [2π+2σ]-cycloadduct **3aa** was generated in 82% isolated yield when **1a** (1.0 equiv) and **2a** (2.0 equiv) were treated with 5 mol% AgOTf in $CHCl_3$ at 0 °C (Table 1, entry 1). The evaluation of ratios of the starting materials showed that the use of onefold excess of **2a** proved efficient for this transformation (entry1 *versus* entries 2−3). The reactions with commonly used Brønsted and oxygenophilic Lewis acids including TfOH, $NHTf_2$, $Ga(OTf)_3$, $Sc(OTf)_3$, $FeCl_3$, $AlCl_3$ and others failed to give the cycloadduct **3aa** or afforded desired product with poor yield (<8% NMR yield) (not shown; see the Supporting Information for the complete set of optimization data). The survey of silver salts revealed that the utilization of $AgBF_4$, $AgSbF_6$, $AgClO_4$ and $AgSO_3CH_3$ all gave inferior outcomes (entries 4−7). The solvent also had a substantial effect on the product distribution but no improvement over $CHCl_3$ was seen (entries 8−9). Lowering the temperature to 0 °C (entry 9 versus 10) was crucial to suppress the competitive side reactions, such as the decomposition of BCB **1a** into cyclobutene **4a** and the nucleophilic opening of BCB.

With the optimal reaction conditions determined, we first investigated the scope of BCBs **1** for this dearomative [2π+2σ] cloadditions (Table 2). This protocol is amenable to a variety of 1,3-disubstituted BCB esters, including methyl (**1a**), ethyl (**1b**), *tert*-butyl (**1c**), benzyl (**1d**) and phenyl (**1e**) esters. Apart from BCB esters, Weinreb amide derived BCB **1f**, which provides a potential handle for further downstream modifications, was compatible, giving the corresponding pentasubstituted BCHs in reasonable yield. As expected, ketones (**1g-1i**), which have stronger electron-withdrawing property than esters and amides, resulted in higher activity (90-99% yield) for the [2π+2σ] cloadditions. The reaction with monosubstituted BCB (**1r** and **1s**) did not afford the cyclized products. Subsequently, an array of substituents at the aromatic ring of BCB esters

Table 1. Selected Examples of the Optimization of the Dearomative [2π+2σ] Cyloadditions[a]

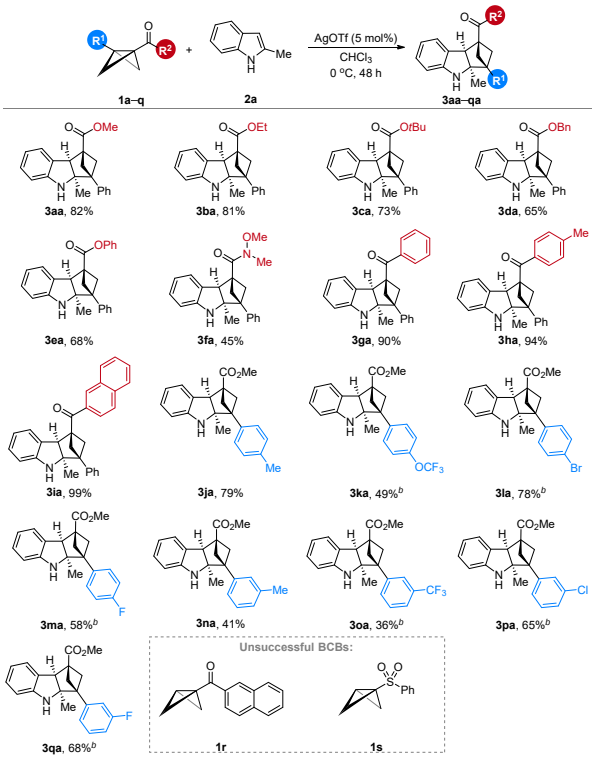


entry	deviation from standard conditions	yield (%)[b]	
		3aa	**4a**
1	none	84	<2
2	**1a** (2.0 equiv), **2a** (1.0 equiv)	69	2
3[c]	**1a** (1.2 equiv), **2a** (1.0 equiv)	56	0
4[c,d]	$AgBF_4$ instead of AgOTf	48	8
5[c,d]	$AgSbF_6$ instead of AgOTf	25	4
6[c,d]	$AgClO_4$ instead of AgOTf	34	2
7[c,d]	$AgSO_3CH_3$ instead of AgOTf	0	0
8[c,d]	$AgBF_4$ instead of AgOTf in CH_2Cl_2	38	5
9[c,d]	$AgBF_4$ instead of AgOTf in toluene	25	3
10[c,d,e]	$AgBF_4$ instead of AgOTf in toluene	14	7

[a] The reactions were performed with **1a** (1.0 equiv), **2a** (2.0 equiv) and AgOTf (5 mol%) in $CHCl_3$ at 0 °C for 48 h. [b] NMR yield with CH_2Br_2 as an internal standard. [c] Reaction time: 12 h. [d] **1a** (1.2 equiv) and **2a** (1.0 equiv) were used. [e] run at 25 °C.

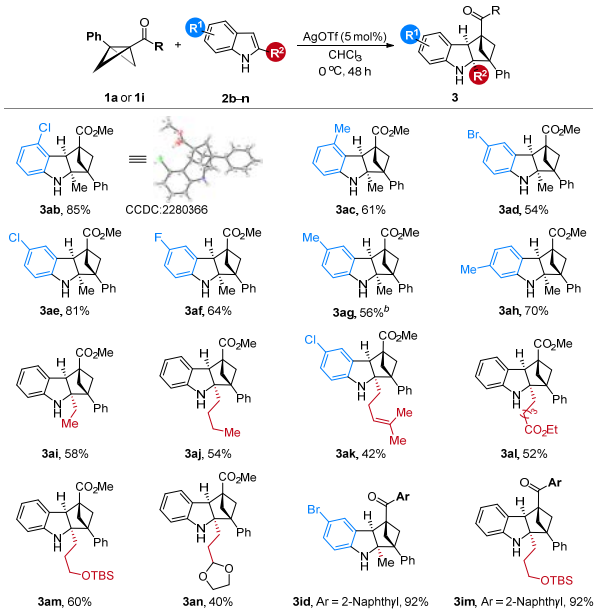
have been examined. The reaction of *para*-substituted phenyl bicyclo[1.1.0]butanes with different substituents on the aryl ring, including alkyl (**1j**), bromo (**1l**), fluoro (**1m**) and trifluoromethyloxy (**1k**) which are popular in drugs and in agrochemicals, proceeded with good efficiency (**3ja**−**3ma**); Furthermore, BCBs with substituents at the *meta*-position of the aryl ring were tolerated under the current conditions, resulting in the formation of the aimed fused BCHs in moderate to good yields (**3na**−**3qa**).

Table 2. Survey the Scope of BCBs[a]



[a] The reactions were performed with **1a** (0.3 mmol), **2a** (0.6 mmol) and AgOTf (5 mol%) in $CHCl_3$ (3.0 mL) at 0 °C for 48 h. [b]Reaction time: 72 h.

Table 3. Survey the Scope of Indoles[a]

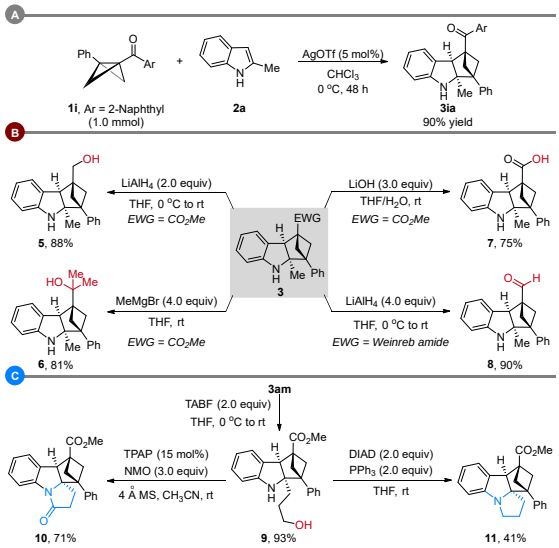


For footnotes a-b, see Table 2.

The scope and generality of this dearomative [2π+2σ] cloaddditions in terms of indole substitution with representative BCBs (**1a** and **1i**) is summarized in Table 3. This method is amenable to a series of 2-methyl-1*H*-indoles bearing different R^1 substituents, including chloro (**2b** and **2e**), alkyl (**2c**, **2g** and **2h**), bromo (**2d**) and fluoro (**2f**) groups at the C4−C6 positions of indoles, and led to the corresponding fused BCHs in moderate to excellent yields (54−85%) as single *cis*-fused diastereomers. The structure of the products **3ab** and **3ac** were established by X-ray crystallographic analysis.[17] The stereochemistry of other C2,C3-fused indoline products, which are widely present as core structures in a large number of natural products and biologically active molecules,[12] were then assigned accordingly. Moreover, this efficient dearomatization reaction was not limited to 2-methyl-1*H*-indole **2a**, its derivatives **2i**–**n** with a variety of functional groups on R^2 moieties, including an alkyl (as in **3ai** and **3aj**), an alkene (as in **3ak**), an ester (as in **3al**), a silyl ether (as in **3am**) and an acetal (as in **3an**) were also compatible with our catalytic system. Again, the utilization of a BCB ketone cycloaddition partner offers a higher yield (92%) to synthesize functionalized BCHs (**3id** and **3im**).

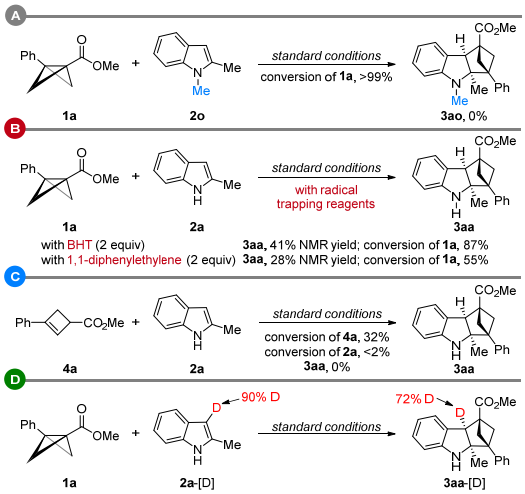
The reaction proved to be easily scalable and was performed on a preparative scale (1.0 mmol) almost without loss in efficiency, furnishing highly decorated BCH **3ia** with two quaternary carbon centers at the bridgehead positions in 90% yield (Scheme 2A). The rich functionalities in the BCHs provide many opportunities for further synthetic transformations. Reduction of the ester group in **3aa** using $LiAlH_4$ provided the primary alcohol **5** in 88% yield. **3aa** can undergo addition reaction with Grignard reagent to give tertiary alcohol **6**. Hydrolysis of ester group of **3aa** afforded the free carboxylic acid **7**. Besides, aldehyde formation by the addition of $LiAlH_4$ to Weinreb amide **3fa** gave **8** in 90% yield (Scheme 2B). Moreover, the silyl group in **3am** could be removed with TBAF to give the primary alcohol **9**. Notably, polycyclic pyrrolizidinone derivative **10** and pyrrolizidine alkaloid **11**[18] featuring a bridged ring system can be synthesized through intramolecular Ley oxidation and Mitsunobu reaction, respectively (Scheme 2C).

Scheme 2. Scale-Up Synthesis and Synthetic Transformations



To interrogate the mechanism, an array of control experiments were conducted. The aimed reaction did not occur when 1,2-dimethylindole **2o** was employed and **1a** decomposed (Scheme 3A). When indole **2a** was treated with BCB **1a** and AgOTf in the presence of BHT or 1,1-diphenylethylene,

Scheme 3. Mechanistic Experiments



the cycloaddition was not completely inhibited, implying that a radical process is not involved in the transformation (Scheme 3B). To rule out the possibility of cycloadduct formation *via* the intermediacy of cyclobutene, **2a** and **4a** were subjected to the current reaction conditions. However, the desired BCH product **3aa** was not observed, thereby confirming that the reaction was not proceeding *via* the cyclobutene intermediate (Scheme 3C). When deuterium-labeled indole **2a**-[D] was used, the monodeuterated product **3aa** with 72% deuteration at 3-position was obtained (Scheme 3D). Though the exact mechanism remains unclear at the current stage, preliminary mechanistic experiments reveal that a concerted [2π+2σ] pathway enabled by silver catalysis or an indoline C3-Ag intermediate may be involved.[19]

In summary, we have developed a platform for dearomative [2π+2σ] cycloaddition of *N*-unprotected 2-substituted indoles and bicyclobutanes *via* silver catalysis. The reaction proceeds under mild conditions with high functional group tolerance and broad substrate scope. The potential synthetic utility and practicality of the approach were also highlighted by the scale-up experiment and the synthetic transformation of the product into other less accessible indoline fused BCHs bearing three quaternary carbon centers, including polycyclic pyrrolizidine alkaloids and functionalized cyclopenta[*b*]indolines. Given the novel reactivity of this cycloaddition and the high demand for strained bicyclic scaffolds as bioisosteres, we envision that this methodology will have a positive impact in both synthetic and medicinal chemistry. Further studies of the mechanism and synthetic applications of this new process are underway.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org

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Notes

The authors declare no competing financial interests.

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