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#### Introduction

C(sp<sup>2</sup>)–H cyclobutylation of hydroxyarenes enabled by silver- $\pi$ -acid catalysis: diastereocontrolled synthesis of 1,3difunctionalized cyclobutanes<sup>†</sup>

Lei Tang, (1); Qi-Nan Huang, (1); Feng Wu, (1); Yuanjiu Xiao, (1); Jin-Lan Zhou, (1); Tong-Tong Xu, (1); Wen-Biao Wu, (1); Shuanglin Qu (1); and Jian-Jun Feng (1); Xiang (1); X

Ring-opening of bicyclo[1.1.0]butanes (BCBs) is emerging as a powerful strategy for 1,3-difunctionalized cyclobutane synthesis. However, reported radical strain-release reactions are typically plagued with diastereoselectivity issues. Herein, an atom-economic protocol for the highly chemo- and diastereoselective polar strain-release ring-opening of BCBs with hydroxyarenes catalyzed by a  $\pi$ -acid catalyst AgBF<sub>4</sub> has been developed. The use of readily available starting materials, low catalyst loading, high selectivity (up to >98:2 d.r.), a broad substrate scope, ease of scale-up, and versatile functionalizations of the cyclobutane products make this approach very attractive for the synthesis of 1,1,3-trisubstituted cyclobutanes. Moreover, control experiments and theoretical calculations were performed to illustrate the reaction mechanism and selectivity.

Cyclobutanes represent important structural units in natural products and other biologically significant molecules.<sup>1</sup> Moreover, the cyclobutane scaffold, especially the 1,3-difunctionalized cyclobutane skeleton, is often incorporated in drug design, such as PF-03654746,<sup>2</sup> linsitinib,<sup>3</sup> and TAK-828F<sup>4</sup> (Scheme 1A). In these cases, a 1,3-substituted cyclobutane linker can act as an aryl isostere with reduced planarity; flexible ethyl- or propyllinkers can also be replaced by conformationally restricted 1,3-disubstituted cyclobutanes to limit the number of possible conformations.<sup>1b</sup> Despite the importance of these cyclobutanes, catalytic methods for their synthesis remained relatively less explored in parallel with their homologues.5-7 Moreover, diastereocontrolled synthesis of 1,1,3-trisubstituted cyclobutanes featuring quaternary carbon stereocenters remains challenging.7

In recent years, strain-release driven transformations have recaptured significant attention in synthetic organic chemistry,<sup>8</sup> materials science,<sup>9</sup> analytical chemistry<sup>10</sup> and bioconjugation.<sup>11</sup>

‡ These authors contributed equally.

release of ring tension embedded in BCBs, coupled with the  $\pi$ type reactivity for the central C–C  $\sigma$ -bond, allows for the design or discovery of new reactions for the synthesis of ring systems.13 Among them, ring-opening reactions via homo- or heterolysis of the spring-loaded C-C bond represent powerful tools enabling quick and efficient access to multisubstituted cyclobutane derivatives. In this direction, there are six general strategies for intermolecular ring-opening reactions of BCBs: (1) radical strain-release reactions with radical nucleophiles. This strategy provides powerful methods for making mostly 1,3-disubstituted alkylated cyclobutanes, albeit mainly with poor diastereoselectivity (not shown).7e,14 (2) Polar strain-release reactions with 2-electron-based nucleophiles. The nucleophilic ring opening reactions of BCBs concerned mainly the addition of various heteroatom (O, N, P)-centred nucleophiles,15 such as Hoz's O-cyclobutylation,<sup>15α</sup> Aggarwal's α-selective ring-opening,<sup>15b</sup> Gaoni's azidation,<sup>15c</sup> Baran's amination,<sup>15d</sup> Wipf's hydrophosphination<sup>15e</sup> and others.<sup>15f</sup> By contrast, the successful use of carbon nucleophilic reagents in addition reactions to BCBs still lags behind and had been limited to strong nucleophiles like organocuprates.7a-d Once again, poor diastereoselectivity was detected in these examples (not shown). (3) Simultaneous activation of BCBs by nucleophiles and electrophiles. This method usually relies on the 1,2-migration process of BCB-boronate complexes, and functionalization by capture of an electrophile, thereby leading to 1,1,3-trisubstituted

As the smallest of fused carbocycles, bicyclo[1.1.0]butanes

(BCBs) are highly strained (ring strain energy  $\sim 66 \text{ kcal mol}^{-1}$ ) yet bench-stable, synthetically versatile carbocycles.<sup>12</sup> The

State Key Laboratory of Chemo/Biosensing and Chemometrics, Advanced Catalytic Engineering Research Center of the Ministry of Education, College of Chemistry and Chemical Engineering, Hunan University, Changsha, Hunan 410082, P. R. China. E-mail: 1334154923@qq.com; squ@hnu.edu.cn; jianjunfeng@hnu.edu.cn

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Scheme 1 Transition metal catalyzed ring-opening reactions of BCBs for the synthesis of cyclobutane derivatives and their scientific context.

cyclobutane products with moderated to excellent diastereoselectivity (Scheme 1B-I).<sup>7*F*-*h*</sup> (4) Palladium hydride enabled hydroalkenylation of BCBs to afford 1,1-disubstituted cyclobutanes (Scheme 1B-II).<sup>16</sup> (5) Polarity-reversal strategy. In 2020, Gryko's group disclosed elegant work on Umpolung BCB activation with Co(1) complexes. Co(1)-catalysis allowed the *in situ* formation of nucleophilic cyclobutyl radicals upon light-driven homolysis of the intermediate Co(11)–alkyl species. This can react with electrophiles to give 1,3-disubstituted cyclobutanes with up to a 75 : 25 d.r. value (Scheme 1B-III).<sup>17</sup> Besides these, (6) oxygenophilic Lewis acid catalyzed ring-opening reactions of BCBs with electrophiles and final intramolecular E1 elimination giving rise to cyclobutene products (Scheme 1B-IV).<sup>18</sup>

Despite significant progress, the above strategies are typically plagued with diastereoselectivity issues. Among them, the known strategy to solve the diastereoselectivity issues and synthesize 1,1,3-trisubstituted cyclobutanes had been limited to palladium and oxygenophilic bismuth Lewis acid catalysis, which were developed by Aggarwal's group<sup>7f,h</sup> and Biju's group, respectively.<sup>19</sup> Therefore, the development of novel transition metal catalyzed methodologies and exploration of further reaction pathways of BCBs is of great value to BCB chemistry.

In the 1970s, Paquette<sup>20a,b</sup> and others<sup>20c-e</sup> have shown that BCBs are capable of silver catalyzed rearrangements. Mechanistic studies suggested that the argento cationic intermediate formed by cleavage of an edge bond of BCBs could further undergo rearrangement to generate 1,3-dienes (Scheme 1C). On the basis of our experience in strained ring chemistry<sup>21</sup> and in order to expand the library of known BCBs, we envisioned that such a carbophilic silver catalysis strategy would enable a different approach to access the cyclobutyl cations from direct activation of the central bond of BCBs. The capture of this intermediate with a naphthol (or phenol) would lead to the formation of the aimed 1,1,3-trisubstituted cyclobutane via Friedel–Crafts-type *C*-alkylation and protodemetalation. However, there are challenges associated with this hypothesis:

(i) the issue of site-selectivity (C–C bond cleavage: edge bond *versus* central bond);<sup>20</sup> (ii) the chemoselectivity issue (*C- versus O*-cyclobutylation);<sup>15*a,b*</sup> (iii) the competitive bicyclobutane-to-cyclobutene isomerization.<sup>18</sup> Besides these, (iv) the other problem that needs to be solved is the control of the diastereoselectivity.

#### **Results and discussion**

To test the hypothesis, we initiated our investigation from the reaction of BCB 1a and 2-naphthol (2a). After screening of various reaction parameters, we found that the desired  $C(sp^2)$ -H cyclobutylation occurred with  $AgBF_4$  (2.5 mol%) as the catalyst in toluene/DCE (1:1) at 100 °C; cis-3aa was obtained in 85% NMR yield with a 95:5 d.r. value along with 11% NMR yield of 4a resulting from isomerization of 1a (Table 1, entry 1). Control experiments showed that both the amount and type of silver salt and the solvent are essential (entries 2-5). The reactions with commonly used Brønsted and oxygenophilic Lewis acid including TfOH, TsOH, Ga(OTf)<sub>3</sub>, Sc(OTf)<sub>3</sub>, Cu(OTf)<sub>2</sub>, and FeCl<sub>3</sub> afforded desired products with poor yield and diastereoselectivity (entries 6-8; see the ESI<sup>†</sup> for the complete set of optimization data). Of note, when Zn(OTf)2 was employed, 63% NMR yield of O-nucleophilic ring-opening product 5aa was obtained as the major product (entry 9).

Under the optimized conditions, we next explored the substrate scope of BCBs as summarized in Table 2. We firstly examined the nature of the ester group and both alkyl (**3aa-3ca**, entries 1–3) and benzyl (entry 4, **3da**) esters were obtained in good yield with good to excellent diastereoselectivity. The reaction of phenyl ester **1e** was also successful yet with eroded diastereoselectivity (entry 5). Different from Biju's work, apart from BCB esters, 1,3-disubstituted bicyclobutanes bearing other electron-withdrawing groups such as BCB ketone **1f**, Weinreb amide derived BCB **1g** and sulfonyl BCB **1h** provided the corresponding ring-opening products in acceptable yield with up

#### Table 1 Selected examples of the optimization of C(sp<sup>2</sup>)–H cyclobutylation<sup>a</sup>



Entry	Variation	<i>cis</i> -3aa $y^{b}$ (%) (d.r. = <i>cis/trans</i> )	$4a y^b (\%)$	<b>5aa</b> $y^{b}$ (%)
1	None	85 (95:5)	11	0
$2^c$	10 mol% AgBF <sub>4</sub> was used	73 (94:6)	14	0
3 <sup>c</sup>	10 mol% AgBF <sub>4</sub> in toluene	78 (91:9)	17	0
$4^c$	10 mol% $AgBF_4$ in DCE	51 (94.5:5.5)	9	0
$5^d$	AgOTf instead of AgBF <sub>4</sub>	61 (83:17)	18	0
$6^d$	TfOH instead of AgBF₄	0	0	0
$7^d$	TsOH $\cdot$ H <sub>2</sub> O instead of AgBF <sub>4</sub>	75 (77:23)	8	0
$8^d$	$Ga(OTf)_3$ instead of AgBF <sub>4</sub>	37 (77:23)	0	0
$9^d$	$Zn(OTf)_2$ instead of AgBF <sub>4</sub>	9 (62:38)	31	63

<sup>*a*</sup> The reactions were performed with **1a** (1.2 equiv.), **2a** (1.0 equiv.) and AgBF<sub>4</sub> (2.5 mol%) in toluene/1,2-dichloroethane(DCE) (1 : 1, v/v) at 100 °C for 3 h. <sup>*b*</sup> NMR yield with CH<sub>2</sub>Br<sub>2</sub> as an internal standard. <sup>*c*</sup> **1a** (1.1 equiv.) was used. <sup>*d*</sup> **1a** (1.1 equiv.), **2a** (1.0 equiv.) and the catalyst (10 mol%) in toluene at 80 °C for 12 h.

Table 2 Survey of the scope of BCBs<sup>a</sup>

$R^{1} \longrightarrow EWG + U \longrightarrow OH \qquad AgBF_{4} (2.5 \text{ mol}\%) \qquad R^{1} \longrightarrow EWG$ toluene/DCE 1:1 100 °C, 3 h 3aa-na						
Entry	$R^1$	EWG	Yield <sup><math>b</math></sup> (%)	d.r. <sup><i>c</i></sup>		
1	Ph	CO <sub>2</sub> Me	80 ( <b>3aa</b> )	95:5		
2	Ph	CO <sub>2</sub> Et	80 ( <b>3ba</b> )	93:7		
3	Ph	CO <sub>2</sub> <i>i</i> Pr	76 ( <b>3ca</b> )	90:10		
4	Ph	CO <sub>2</sub> Bn	77 ( <b>3da</b> )	93:7		
5	Ph	CO <sub>2</sub> Ph	64 ( <b>3ea</b> )	81:19		
6	Ph	C(O)(2-naphthyl)	50 $(3fa)^d$	86:14		
7	Ph	C(O)NMe(OMe)	80 ( <b>3ga</b> )	>98:2		
8	Ph	SO <sub>2</sub> Ph	56 $(3ha)^d$	67:33		
9	4-MeC <sub>6</sub> H <sub>4</sub>	CO <sub>2</sub> Me	76 ( <b>3ia</b> )	>98:2		
10	$4-CF_3OC_6H_4$	CO <sub>2</sub> Me	74 ( <b>3ja</b> )	92:8		
11	$4 - FC_6H_4$	$CO_2Me$	80 ( <b>3ka</b> )	>98:2		
12	4-CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	CO <sub>2</sub> Me	25 ( <b>3la</b> )	>98:2		
13	3-MeC <sub>6</sub> H <sub>4</sub>	CO <sub>2</sub> Me	75 ( <b>3ma</b> )	>98:2		
14	3-FC <sub>c</sub> H <sub>4</sub>	CO <sub>2</sub> Me	$76(3na)^{d}$	80:20		

<sup>a</sup> Unless otherwise noted, the reactions were performed with 1 (0.36 mmol), 2a (0.3 mmol) and AgBF<sub>4</sub> (2.5 mol%) in toluene/1,2dichloroethane(DCE) (1:1, v/v, 2 mL) at 100 °C for 3 h. <sup>b</sup> Isolated yield of *cis*-3. <sup>c</sup> Determined by <sup>1</sup>H NMR spectroscopic analysis of the crude reaction product. <sup>d</sup> Combined isolated yield of the crude reaction product. diastereomers which cannot be separated by chromatography.

to >98:2 d.r. (3fa-3ha, entries 6-8). The sulfonyl group is a localizing electron-withdrawing group, which stabilizes the negative charge by exerting mainly an inductive effect. By contrast, the carbonyl group is a charge delocalizing group.<sup>15a</sup> Notably, sulfonyl BCB is a suitable substrate in our silver- $\pi$ -acid

catalytic system. However, it is not compatible with Biju's oxygenophilic bismuth Lewis acid catalytic system.19 This result implies that the cationic Ag catalyst could preferably activate the bridging C-C bond in BCB without the need to coordinate to the ester oxygen. Subsequently, a variety of substituents at the aromatic ring of BCB esters have been examined. BCBs with substituents in the para- and meta-positions were compatible with our catalyst system and afforded the corresponding 1,1,3trisubstituted cyclobutanes in good yield with up to > 98:2 d.r. (3ia-3na, entries 9-14). The replacement of methyl (1i) by a strongly electron-withdrawing  $CF_3$  group (11) was an exception as the yield decreased from 76% for 3ia to 25% for 3la (entry 9 vs. entry 12). It is probably because the BCB containing an electron-deficient unit can't stabilize the in situ generated cyclobutyl cation.

We then examined the scope of naphthols and phenols (Scheme 2). This method is amenable to a series of 2-naphthols bearing different R<sup>3</sup> substituents, including aryl (2b<sup>22</sup> and 2f), halogen (2c, 2h and 2j), and propargyl (2g) groups at the C4-C7 positions of 2-naphthols, and led to the corresponding trisubstituted cyclobutanes with synthetically useful phenoxy functionalities, in moderate to excellent yields (43-92%) with up to >98:2 d.r. 1-Naphthols also furnished the corresponding product with good yield and excellent diastereoselectivity (2km). Relatively low yields and selectivities were observed with pmethoxy- and phenyl-substituted phenols (3an and 3ao), while 3,5-dimethylphenol (2p) afforded the corresponding product in a good yield and d.r. value.

The reaction proved to be easily scalable and was performed on a preparative scale (1.0 mmol) without any loss in efficiency and selectivity, furnishing the product cis-3am in 81% yield with >98:2 d.r. (Scheme 3). The synthetic utility of the products was

1 24 3' 4<sup>4</sup> 5 6'



Scheme 2 Survey of the scope of naphthols and phenols.<sup>a-d a</sup> The reactions were performed with 1a (0.36 mmol), 2b-p (0.3 mmol) and AgBF₄ (2.5 mol%) in toluene/1,2-dichloroethane(DCE) (1:1, v/v, 2 mL) at 100 °C for 3 h.<sup>b</sup> Isolated yield of cis-3.<sup>c</sup> d.r. value was determined by <sup>1</sup>H NMR spectroscopic analysis of the crude reaction product. <sup>d</sup>Combined isolated yield of the diastereomers which cannot be separated by chromatography

demonstrated by carrying out a series of functional group interconversions of the phenolic hydroxyl- and ester groups. On one hand, a number of different groups, including the phosphine group (7), H (8) and alkyl group (9), could be incorporated into the aromatic ring via cross-coupling after converting the phenoxy group into triflate 6. On the other hand, ester 3aa can undergo addition, hydrolysis and reduction reactions to give tertiary alcohol 9, carboxylic acid 10 and primary alcohol 12 respectively. Notably, 1-benzoxepin derivatives 11 and 13



Cond. A: Ph2P(O)H (4.0 equiv), Pd(OAc)2 (10 mol%), dppb (12 mol%), NEt3, DMSO, 110 °C Cond. B: Et<sub>3</sub>SiH (2.5 equiv), Pd(OAc)<sub>2</sub> (10 mol%), dppp (12 mol%), DMF, 60 °C Cond. C: MeMgBr (5.0 equiv), NiCl<sub>2</sub>(dppp) (5 mol%), Et<sub>2</sub>O, 0 °C to reflux

-20 to 0 °C

Scheme 3 Scale-up synthesis and synthetic transformations.

rt

10: 94%

featuring a bridged ring system can be synthesized through Keck macrolactonization and intramolecular Mitsunobu reactions respectively.

To interrogate the mechanism, a series of control experiments were conducted. The desired reaction did not occur when 2-methoxynaphthalene was employed (Scheme 4A). Moreover, the deuterium labeling experiment confirmed the critical role of the hydroxyl group of naphthol in those C(sp<sup>2</sup>)-H cyclobutylations (Scheme 4B). When 3aa with 75:25 d.r. was applied under the standard conditions, no change in the diastereoselectivity of 3aa was found (see, ESI<sup>†</sup>). This result suggests that high diastereoselectivity may not be obtained via an isomerization pathway (trans- to cis-3aa). The treatment of 4a with standard conditions gave 3aa in 22% NMR yield. However, cyclobutene 4a was far less reactive than bicyclobutane 1a (Scheme 4C versus Table 1 entry 2).

To further elucidate the mechanistic details of this reaction and to explain the observed stereoselectivity, density functional theory (DFT) calculations<sup>23</sup> were carried out on the model reaction of BCB 1a and 2-naphthol (2a) promoted by the silver catalyst. On the basis of the control experiments and DFT calculations, a plausible catalytic cycle for this diastereoselective transformation is summarized in Scheme 5 (we have considered different possible reaction pathways, and only discuss the most favorable one here; for more details see the ESI<sup>†</sup>). The molecular orbital analysis of 1a reveals that the bridging C–C bond exhibits the characteristics of a  $\pi$ -bond (Fig. S1<sup>†</sup>). Thus, the cationic Ag catalyst (a typical  $\pi$ -acid) preferably activates the bridging C-C bond rather than the C=O bond, leading to the ring-opening of BCB and formation of the carbon cation intermediate A (Fig. S2<sup>†</sup>). Then, the nucleophilic attack of A by the  $\pi$ -bond of 2a forms a new C-C bond and affords the intermediate B. Next, another molecule of 2a enters into the reaction with its  $\pi$ -bond coordinating to the  $\pi$ -acidic Ag atom of **B**, followed by 1,3-migration of Ag, leading to a silver enolate intermediate C with a hydrogen bond between the hydroxyl group and the enolate carbon. Subsequently, the proton is facilely transferred from the hydroxyl group to the enolate carbon of the BCB moiety, releasing the naphthol silver salt D and giving the protonated intermediate E. The process from B to E can be viewed as the replacement of the Ag atom by



Scheme 4 Mechanistic experiments.

-Me

'nι

Me

9: 91%

13: 39%

OH

12: 94%

Ph



Scheme 5 Proposed mechanism. The values in brackets are calculated relative Gibbs free energies (in kcal  $mol^{-1}$ ).

the proton. This process would not change the stereochemistry of the BCB carbon, because the substrate **2a** could only approach the BCB ring from the top direction by coordination with the Ag atom (for more energetic and geometric information see Fig. S3 and S4†). In addition, this is in agreement with the deuterium labeling experiment (Scheme 4B) that the proton in the product is from the hydroxyl group of **2a**. Finally, the naphthol anion moiety of **D** abstracts the proton of **E**, producing the final major product *cis*-**3aa** and releasing **F**, in which the  $\pi$ acidic Ag<sup>+</sup> catalyst is coordinated by the  $\pi$ -bond of **2a**.

The DFT studies show that the diastereoselectivity is determined by the nucleophilic attack step  $(\mathbf{A} \rightarrow \mathbf{B})$ , where the nucleophile **2a** approaches the carbocation **A** through either the top or the bottom directions, finally leading to isomers of *trans*and *cis*-**3aa**, respectively. The transition states for these two nucleophilic attack modes are compared. As shown in Scheme 6, there is a hydrogen bond interaction in **TS2**-*cis*, which helps to stabilize this transition state. In contrast, it shows



Scheme 6 Comparison of the two transition states for the formation of *cis*- and *trans*-3aa. The selected bond distances are in Å.

electrostatic repulsion between the acidic hydrogen and the positive Ag center in **TS2-***trans*, which hinders this nucleophilic attack. Thus, **TS2-***cis* is lower than **TS2-***trans* by 3.3 kcal mol<sup>-1</sup>, which well agrees with the experiment that *cis*-**3aa** is the major product. It is of note that the nucleophilic attack could also occur by the oxygen atom of **2a**. However, the calculations show that this *O*-nucleophilic attack is less favorable than both **TS2-***cis* and **TS2-***trans* (Fig. S3 and S5†). In addition, the reaction of cyclobutene **4a** with **2a** to form **3aa** is also examined by DFT calculation, which is predicted to have a higher activation barrier (Fig. S6†), in agreement with lower yields (Scheme 4C).

#### Conclusion

In summary, by taking advantage of hydroxyarenes as C-nucleophiles rather than O-nucleophiles in unusual silver catalyzed polar strain-release ring-opening of BCBs, an atom-economic and highly selective method (up to >98:2 d.r.) for the synthesis of 1,1,3-trisubstituted cyclobutanes was developed. The salient features of this transformation include readily available starting materials, low catalyst loading, wide functional-group compatibility, versatile functionalizations of the cyclobutane products and scalability. Notably, mechanistic experiments and DFT calculations were performed to gain insights into the reaction mechanism, which shows that the silver catalyst acts as a carbophilic  $\pi$ -acid rather than an oxygenophilic Lewis acid to effectively activate the BCB bridging C-C bond and promote the transformation. The diastereoselectivity is determined by hydrogen bond interaction and steric repulsions in the nucleophilic attack step. This reactivity mode may open opportunities for the development of other reaction processes.

### Data availability

All detailed procedures, characterization data, NMR spectra and DFT studies are available in the ESI.†

### Author contributions

L. T., F. W., Y. X., J.-L., Z., and T.-T. X. performed the experiments and conducted the analytical characterization. Q.-N. H. and S. Q. executed the theoretical calculations. W.-B. W., S. Q. and J.-J. F. wrote the manuscript. J.-J. F. conceived the catalytic system.

## Conflicts of interest

There are no conflicts to declare.

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