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C(sp^2)–H Cyclobutylation of hydroxyarenes enabled by silver-π-acid catalysis: diastereocontrolled synthesis of 1,3-difunctionalized cyclobutanes

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Ring-opening of bicyclo[1.1.0]butanes (BCBs) is emerging as a powerful strategy for 1,3-difunctionalized cyclobutanes synthesis. However, the 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 π-acid catalyst $AgBF_4$ has been developed. 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 synthsis of 1,1,3-trisubstituted cyclobutanes. Moreover, control experiments and theoretical calculations were performed to illustrate the reaction mechanism and selectivity.

Introduction

Cyclobutanes represent important structural units in natural product and other biologically significant molecules.[1] Moreover, the cyclobutane scaffold, especially 1,3-difunctionalized cyclobutane skeleton, is often incorporated in drug design, such as PF-03654746,[2] linsitinib,[3] and TAK-828F[4] (Scheme 1A). In these cases, 1,3-substituted cyclobutane linker can act as an aryl isosteres with reduced planarity; flexible ethyl- or propyl-linkers can also be replaced by conformationally restricted 1,3-disubstituted cyclobutanes to limit the number of possible conformations.[1b] 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,[8] materials science,[9] analytical chemistry[10] and bioconjugation.[11] As the smallest of fused carbocycles, bicyclo[1.1.0]butanes (BCBs) are highly strained (ring strain energy ~66 kcal mol^{-1}) yet bench-stable, synthetically versatile carbocycles.[12] The release of ring tension embedded in BCBs, coupled with the π-character for the central C–C σ-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 (Scheme 1B): (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).[7d,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,[15a] Aggarwal's α-selective ring-openings,[15b] Gaoni's azidation,[15c] Baran's amination,[15d] Wipf's hydrophosphination[15e] and others.[15f] By contrast, the successful use of carbon nucleophilic reagents in addition reactions to BCBs still lags behind and had been limited to the strong nucleophiles like organocuprates.[7a-c] 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, therefore leading to the 1,1,3-trisubstituted cyclobutane products with moderated to excellent diastereoselectivity.[7e-g] (4) Palladium hydride enabled hydroalkenylation of BCBs to afford 1,1-disubstituted cyclobutanes.[16] (5) Polarity-reversal strategy. In 2020, Gryko's group disclosed an elegant work on umpolung BCB activation with Co(I) complexes. Co(I)-catalysis allowed the in situ formation of nucleophilic cyclobutyl radicals upon light-

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†Electronic Supplementary Information (ESI) available: Experimental details, characterization, spectroscopic data.

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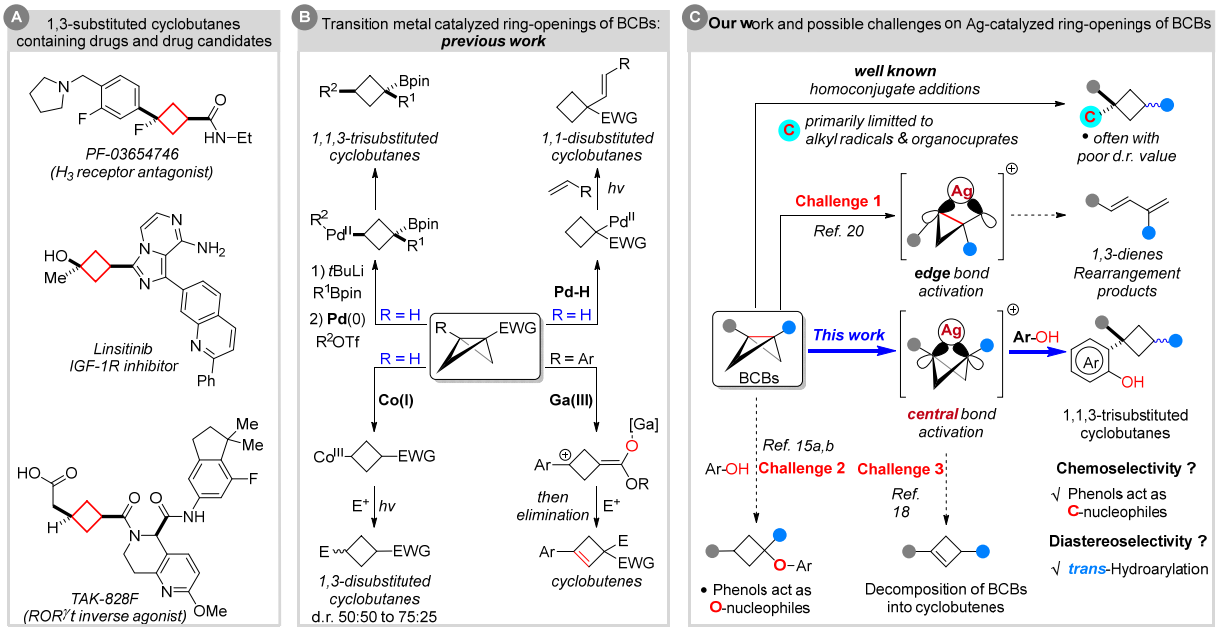


Scheme 1 Transition metal catalyzed ring-opening reactions of BCBs for synthesis of cyclobutane derivatives and its scientific context.

driven homolysis of the intermediate Co(III)–alkyl species. This can react with electrophiles to give 1,3-disubstituted cyclobutanes with up to 75:25 dr value.[17] Besides these, (6) Oxygenophilic Lewis acid catalyzed ring-opening reactions of BCBs with electrophiles and final intramolecular E1 elimination giving rise to the cyclobutene products.[18]

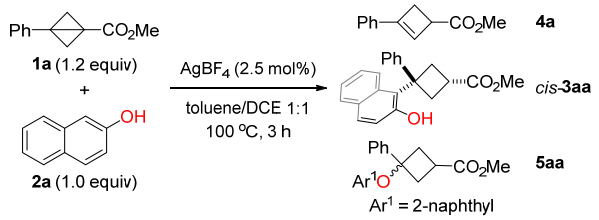
Despite significant progress, the above strategies are typically plagued with diastereoselectivity issues. Among them, the known strategy to solve the diastereoselectivity issues and synthesize 1,1,3-trisubstituted cyclobutanes had been limited to palladium and oxygenophilic bismuth Lewis acid catalysis,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

In 1970s, Paquette[20a,b] and others[20c-e] 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 rings chemistry[21] and in order to expand the library of known BCBs reactivity, we envisioned that such carbophilic silver catalysis strategy would enable a different approach to access the cyclobutyl cations from direct activation of the central bond of BCBs. Capture of this intermediate with a naphthols (or phenols) 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);[20] (ii) the chemoselectivity issue (C- versus O-cyclobutylation);[15a,b] (iii) the competitive bicyclobutane-to-cyclobutene isomerization.[18] Besides these, (iv) the other problem that needs to be solved is how to control 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 catalyst in toluene/DCE (1:1) at 100 °C; *cis*-**3aa** was obtained in 85% NMR yield with 95:5 d.r. value along with 11% NMR yield of **4a** resulting from rapid isomerization of **1a**. (Table1, 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, $Ga(OTf)_3$, $Sc(OTf)_3$, $Cu(OTf)_2$, and $FeCl_3$ afforded desired product with poor yield and diastereoselectivity (entries 6 and 7; see the Supporting Information for the complete set of optimization data). Of note,

Table 1. Selected examples of the optimization of the C(sp^2)-H cyclobutylation.[a]



Entry	Variation	*cis*-**3aa** y(%)[b] (d.r.=cis/trans)	**4a** y(%)[b]	**5aa** y(%)[b]
1	none	85 (95:5)	11	0
2[c]	10 mol% $AgBF_4$ was used	73 (94:6)	14	0
3[c]	10 mol% $AgBF_4$ 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 $AgBF_4$	61 (83:17)	18	0
6[d]	TfOH instead of $AgBF_4$	0	0	0
7[d]	$Ga(OTf)_3$ instead of $AgBF_4$	37 (-)	0	0
8[d]	$Zn(OTf)_2$ instead of $AgBF_4$	9 (-)	31	63

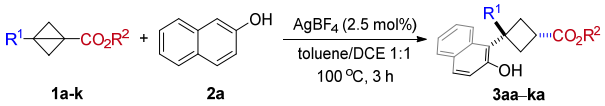
[a] The reactions were performed with **1a** (1.2 equiv), **2a** (1.0 equiv) and $AgBF_4$ (2.5 mol%) in toluene/1,2-dichloroethane(DCE) (1:1) at 100 °C for 3 h. [b] NMR yield with CH_2Br_2 as an internal standard. [c] **1a** (1.1 equiv) was used. [d] **1a** (1.1 equiv), **2a** (1.0 equiv) and catalyst (10 mol%) in toluene at 80 °C for 12 h.

when $Zn(OTf)_2$ was employed, 63% NMR yield of O-nucleophilic ring-opening product **5aa** was obtained as the major product.

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). 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 1,1,3-trisubstituted cyclobutanes in good yield with up to > 98:2 d.r. (**3fa**-**3ka**, entries 6-11). Replacement of methyl (**1f**) by a strongly electron-withdrawing CF_3 group (**1i**) was a little exception as the yield decreased from 76% for **3fa** to 25% for **3ia** (entry 6 *vs.* entry 9). It is probably due to 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^3 substituents, including aryl (**2b** 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 (**2k**-

Table 2. Survey the scope of BCBs.[a]



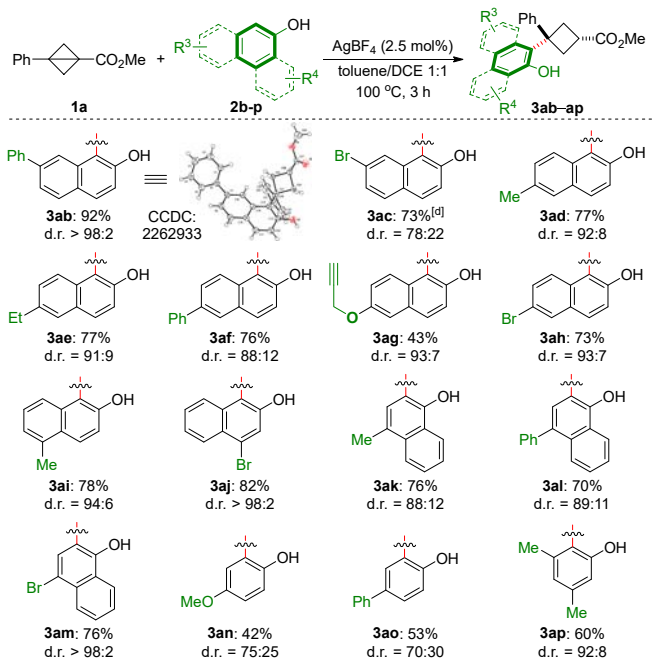
Entry	R^1	R^2	Yield (%)[b]	d.r.[c]
1	Ph	Me	80 (**3aa**)	95:5
2	Ph	Et	80 (**3ba**)	93:7
3	Ph	*i*Pr	76 (**3ca**)	90:10
4	Ph	Bn	77 (**3da**)	93:7
5	Ph	Ph	64 (**3ea**)	81:19
6	4-MeC_6H_4	Me	76 (**3fa**)	>98:2
7	4-$CF_3OC_6H_4$	Me	74 (**3ga**)	92:8
8	4-FC_6H_4	Me	80 (**3ha**)	>98:2
9	4-$CF_3C_6H_4$	Me	25 (**3ia**)	>98:2
10	3-MeC_6H_4	Me	75 (**3ja**)	>98:2
11	3-FC_6H_4	Me	76 (**3ka**)[d]	80:20

[a] Unless otherwise noted, the reactions were performed with **1** (0.36 mmol), **2a** (0.3 mmol) and $AgBF_4$ (2.5 mol%) in toluene/1,2-dichloroethane(DCE) (1:1, 2 mL) at 100 °C for 3 h. [b] Isolated yield of *cis*-**3**. [c] Determined by ^1H NMR spectroscopic analysis of the crude reaction product. [d] Combined isolated yield of the diastereomers which cannot be separated by chromatography.

m). Relatively low yields and selectivities were observed with *p*-methoxy- 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 product *cis*-**3am** in 81% yield with >98:2 d.r. (Scheme 3). The synthetic utility of the products was 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 phosphine group (**7**), H (**8**) and alkyl group (**9**), could be incorporated into the aromatic ring via cross-couplings 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** featuring a bridged ring system can be synthesized through Keck macrolactonization and intramolecular Mitsunobu reaction respectively.

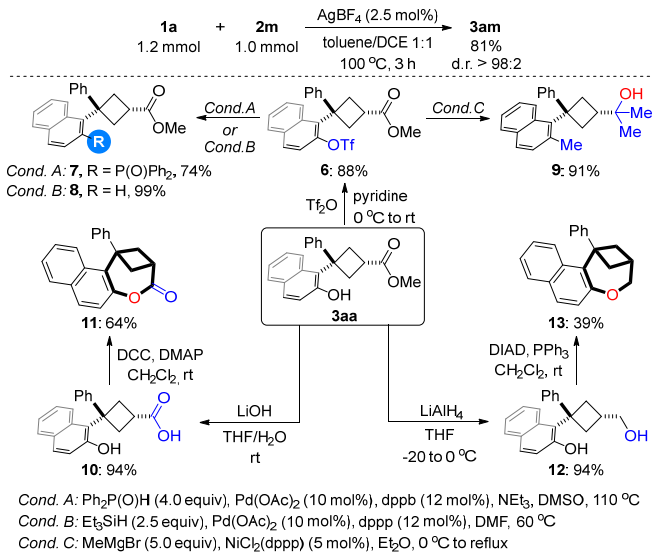
To interrogate the mechanism, a series of control experiments were conducted. The desired reaction did not occur when 2-methoxynaphthalene was employed (Scheme 4A). Moreover, the deuterium labeling experiment confirmed the critical role of the hydroxyl group of naphthol in those C(sp^2)-H cyclobutylations (Scheme 4B). When **3aa** with 75:25 d.r. was applied under the standard conditions, no change in



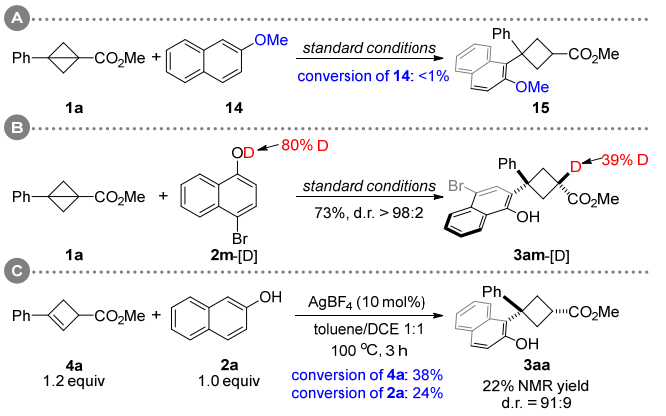
Scheme 2 Survey the scope of naphthols and phenols.[a-c] For footnotes a–c, see Table 2.

diastereoselectivity of **3aa** was found (not shown). This result suggests that high diastereoselectivity might not be able to obtain *via* an isomerization pathway (*trans*- to *cis*-**3aa**). 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 Table1 entry 2).

To further elucidate the mechanistic details of this reaction and to explain the observed stereoselectivity, Density functional theory (DFT) calculations[23] 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. The molecular orbital analysis of **1a** reveals that the bridging C-



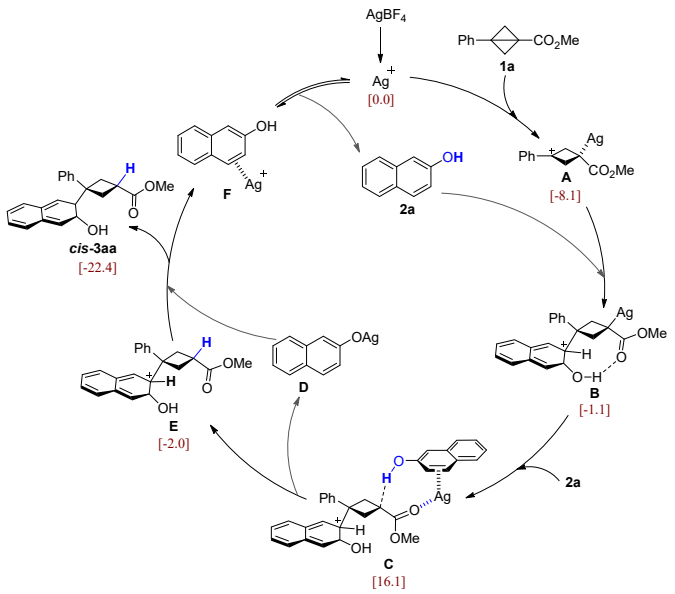
Scheme 3 Scale-up synthesis and synthetic transformations.



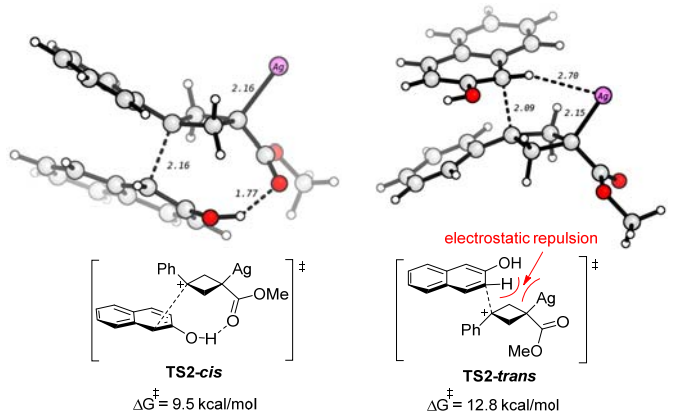
Scheme 4 Mechanistic experiments.

C bond exhibits characteristics of a π-bond (Figure S1). Thus, the cationic Ag catalyst (a typical π-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** (details see Figure S2). Then, the nucleophilic attack of **A** by the π-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 π-bond coordinating to the π-acidic Ag atom of **B**, followed by the 1,3-migration of Ag, while the hydroxyl group of **2a** forms a hydrogen bond with the anionic BCB carbon, giving intermediate **C** (details see Figure S3). Subsequently, the proton is facilely transferred from the naphthol moiety to the BCB carbon, releasing the naphthol silver salt **D** and leading to the protanated intermediate **E**. This is in agreement with deuterium labeling experiment (Scheme 4B). Finally, the naphthol anion of **D** abstracts the proton of **E**, producing the final major product *cis*-**3aa** and releasing **F**, in which the π-acidic Ag^+ catalyst is coordinated by the π-bond of **2a**. We have also considered other possible activation modes or side reactions, and all the energetic details are provided in the ESI.

The DFT studies show that the diastereoselectivity is determined by the nucleophilic attack step (**A**→**B**), where the nucleophile **2a** could approaches the carbon cation **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 **TS4-*cis***, which helps to stabilize this transition state. On the contrary, it shows electrostatic repulsion between the acidic hydrogen and the positive Ag center in **TS4-*trans***, which hinders this nucleophilic attack. Thus, **TS4-*cis*** is lower than **TS4-*trans*** by 3.3 kcal/mol, which well agrees the experiment that the *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 **TS4-*cis*** and **TS4-*trans*** (Figure S3 and Figure S4). 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 (Figure S5), in agreement with lower yields (Scheme 4c).



Scheme 5. Proposed mechanism. The values in brackets are calculated relative Gibbs free energies (in kcal/mol).



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

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 π-acid rather than 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.

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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22 Deposition numbers 2262933 (for *cis*-**3ab**) 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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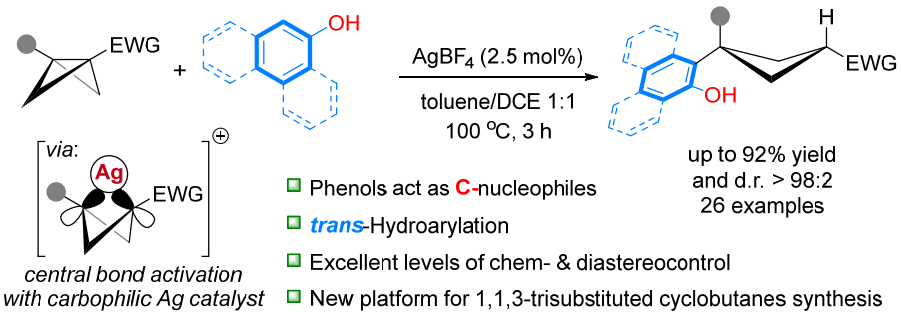
TOC



A carbophilic silver Lewis acid catalyzes polar strain-release ring-opening of BCBs with hydroxyarenes to afford 1,1,3-trisubstituted cyclobutanes in high yields and excellent chemo- and diastereoselectivity.