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C(sp²)-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 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 π -acid catalyst AgBF₄ 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.

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Introduction

Cyclobutanes represent important structural units in natural products and other biologically significant molecules.¹ Moreover, the cyclobutane scaffold, especially the 1,3-difunctionalized cyclobutane skeleton, is often incorporated in drug design, such as PF-03654746,² linsitinib,³ and TAK-828F⁴ (Scheme 1A). In these cases, a 1,3-substituted cyclobutane linker can act as an aryl isostere 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 chemistry¹⁰ and bioconjugation.¹¹

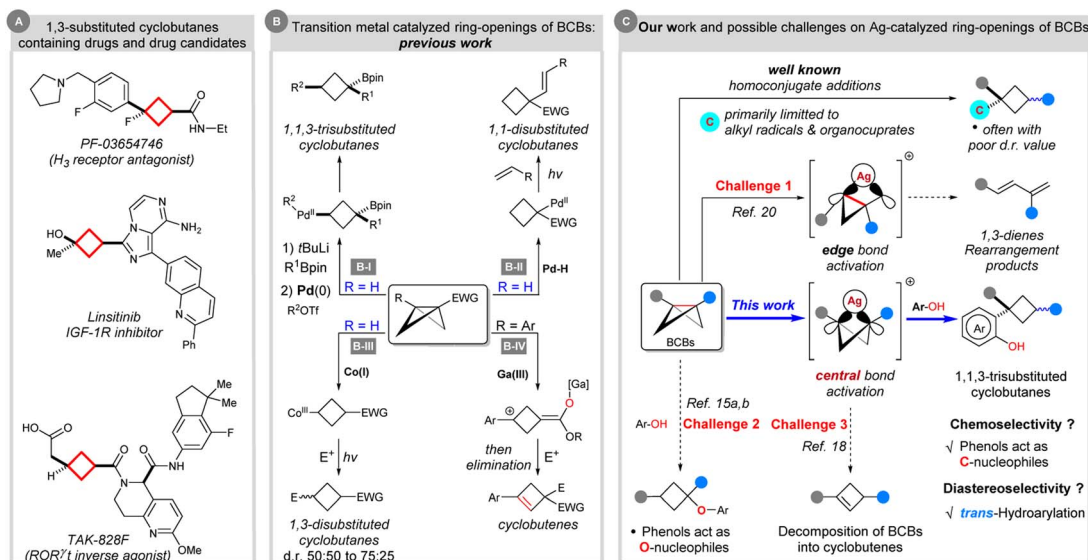
As the smallest of fused carbocycles, bicyclo[1.1.0]butanes (BCBs) are highly strained (ring strain energy \sim 66 kcal mol⁻¹) yet bench-stable, synthetically versatile carbocycles.¹² The release of ring tension embedded in BCBs, coupled with the π -type reactivity for the central C-C σ -bond, allows 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: (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).^{7c,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-opening,^{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 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

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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).^{7f-h} (4) Palladium hydride enabled hydroalkenylation of BCBs to afford 1,1-disubstituted cyclobutanes (Scheme 1B-II).¹⁶ (5) Polarity-reversal strategy. In 2020, Gryko's group disclosed elegant work on Umpolung BCB activation with Co(I) complexes. Co(I)-catalysis allowed the *in situ* formation of nucleophilic cyclobutyl radicals upon light-driven homolysis of the intermediate Co(III)-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).¹⁷ 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).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^{7f,h} 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 BCB chemistry.

In the 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 ring chemistry²¹ 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:

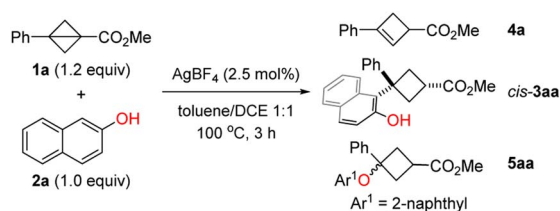
(i) the issue of site-selectivity (C–C bond cleavage: edge bond *versus* central bond);²⁰ (ii) the chemoselectivity issue (*C*- *versus* *O*-cyclobutylation);^{15a,b} (iii) the competitive bicyclobutane-to-cyclobutene isomerization.¹⁸ Besides these, (iv) the other problem that needs to be solved is the 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(sp²)-H cyclobutylation occurred with AgBF₄ (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)₃, Sc(OTf)₃, Cu(OTf)₂, and FeCl₃ afforded desired products with poor yield and diastereoselectivity (entries 6–8; see the ESI† 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).

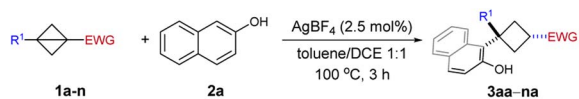
Under the optimized conditions, we next explored the substrate scope of BCBs as summarized in Table 2. We firstly examined the nature of the ester group and both alkyl (**3aa–3ca**, entries 1–3) and benzyl (entry 4, **3da**) esters were obtained in good yield with good to excellent diastereoselectivity. 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(sp²)-H cyclobutylation^a

Entry	Variation	<i>cis-3aa</i> <i>y</i> ^b (%) (d.r. = <i>cis/trans</i>)	4a <i>y</i> ^b (%)	5aa <i>y</i> ^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	TsOH·H ₂ O instead of AgBF ₄	75 (77 : 23)	8	0
8 ^d	Ga(OTf) ₃ instead of AgBF ₄	37 (77 : 23)	0	0
9 ^d	Zn(OTf) ₂ instead of AgBF ₄	9 (62 : 38)	31	63

^a The reactions were performed with **1a** (1.2 equiv.), **2a** (1.0 equiv.) and AgBF₄ (2.5 mol%) in toluene/1,2-dichloroethane(DCE) (1 : 1, v/v) at 100 °C for 3 h. ^b NMR yield with CH₂Br₂ as an internal standard. ^c **1a** (1.1 equiv.) was used. ^d **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^a

Entry	R ¹	EWG	Yield ^b (%)	d.r. ^c
1	Ph	CO ₂ Me	80 (3aa)	95 : 5
2	Ph	CO ₂ Et	80 (3ba)	93 : 7
3	Ph	CO ₂ <i>i</i> Pr	76 (3ca)	90 : 10
4	Ph	CO ₂ Bn	77 (3da)	93 : 7
5	Ph	CO ₂ Ph	64 (3ea)	81 : 19
6	Ph	C(O)(2-naphthyl)	50 (3fa) ^d	86 : 14
7	Ph	C(O)NMe(OMe)	80 (3ga)	>98 : 2
8	Ph	SO ₂ Ph	56 (3ha) ^d	67 : 33
9	4-MeC ₆ H ₄	CO ₂ Me	76 (3ia)	>98 : 2
10	4-CF ₃ OC ₆ H ₄	CO ₂ Me	74 (3ja)	92 : 8
11	4-FC ₆ H ₄	CO ₂ Me	80 (3ka)	>98 : 2
12	4-CF ₃ C ₆ H ₄	CO ₂ Me	25 (3la)	>98 : 2
13	3-MeC ₆ H ₄	CO ₂ Me	75 (3ma)	>98 : 2
14	3-FC ₆ H ₄	CO ₂ Me	76 (3na) ^d	80 : 20

^a Unless otherwise noted, the reactions were performed with **1** (0.36 mmol), **2a** (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. ^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.

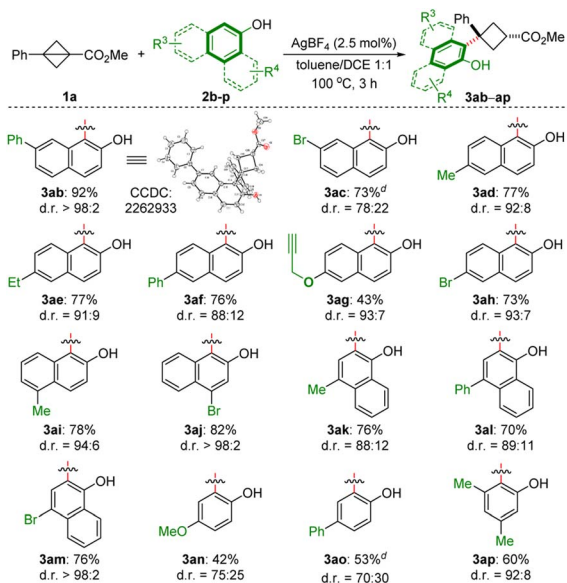
to >98 : 2 d.r. (**3fa-3ha**, entries 6–8). The sulfonyl group is a localizing electron-withdrawing group, which stabilizes the negative charge by exerting mainly an inductive effect. By contrast, the carbonyl group is a charge delocalizing group.^{15a} Notably, sulfonyl BCB is a suitable substrate in our silver- π -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 1,1,3-trisubstituted 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 CF₃ group (**1l**) 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 R³ substituents, including aryl (**2b**²² 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-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.

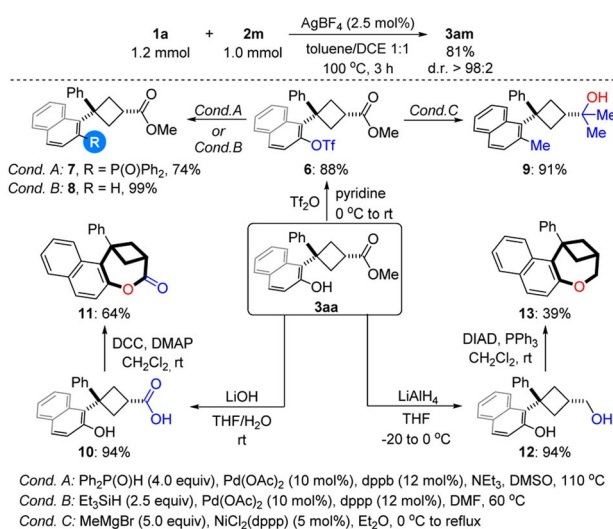
The reaction proved to be easily scalable and was performed on a preparative scale (1.0 mmol) without any loss in efficiency and selectivity, furnishing the product *cis*-**3am** in 81% yield with >98 : 2 d.r. (Scheme 3). The synthetic utility of the products was





Scheme 2 Survey of the scope of naphthols and phenols.^{a-d} ^aThe reactions were performed with **1a** (0.36 mmol), **2b-p** (0.3 mmol) and AgBF_4 (2.5 mol%) in toluene/1,2-dichloroethane(DCE) (1:1, v/v, 2 mL) at 100 °C for 3 h. ^b Isolated yield of *cis*-**3**. ^c d.r. value was determined by ¹H NMR spectroscopic analysis of the crude reaction product. ^d 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**

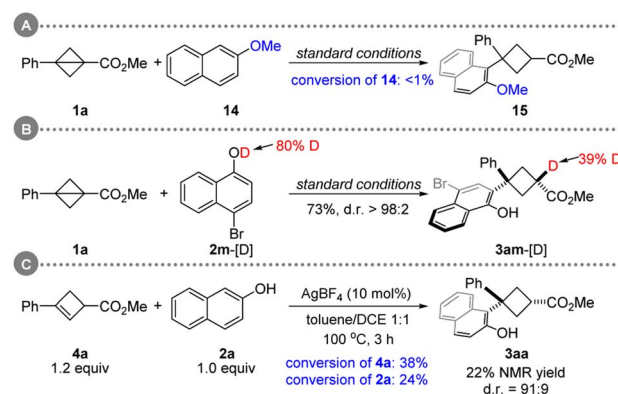


Scheme 3 Scale-up synthesis and synthetic transformations.

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

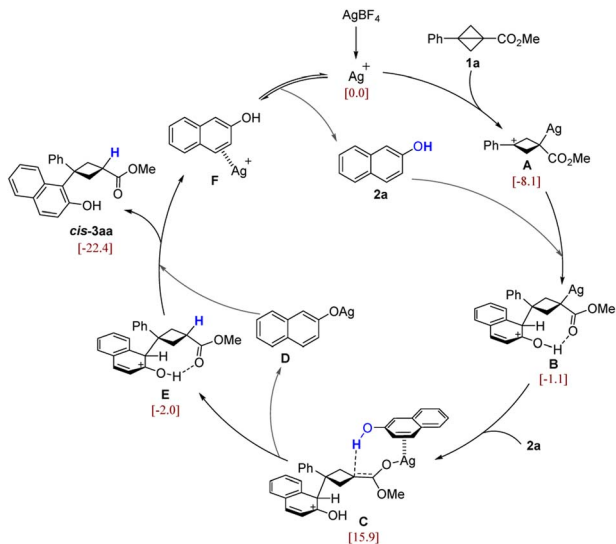
To interrogate the mechanism, a series of control experiments were conducted. The desired reaction did not occur when 2-methoxynaphthalene was employed (Scheme 4A). Moreover, the deuterium labeling experiment confirmed the critical role of the hydroxyl group of naphthol in those $\text{C}(\text{sp}^2)\text{-H}$ 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†). 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) calculations²³ 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†). The molecular orbital analysis of **1a** reveals that the bridging C–C bond exhibits the characteristics of a π -bond (Fig. 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** (Fig. 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 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 readily 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.

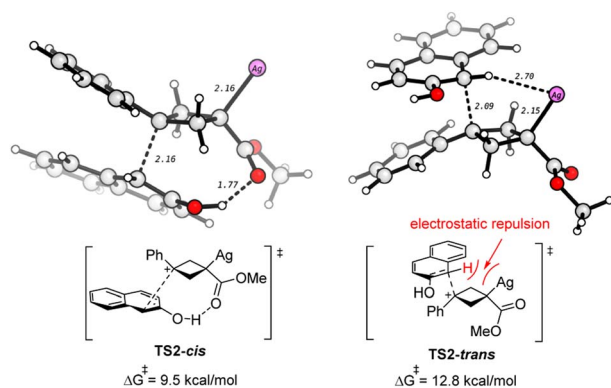




Scheme 5 Proposed mechanism. The values in brackets are calculated relative Gibbs free energies (in kcal mol⁻¹).

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 π-acidic Ag⁺ catalyst is coordinated by the π-bond of **2a**.

The DFT studies show that the diastereoselectivity is determined by the nucleophilic attack step (**A** → **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⁻¹, 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 π-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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References

- 1 (a) C. Hui, Y. Liu, M. Jiang and P. Wu, Cyclobutane-containing scaffolds in bioactive small molecules, *Trends Chem.*, 2022, **4**, 677; (b) M. R. van der Kolk, M. A. C. H. Janssen, F. P. J. T. Rutjes and D. Blanco-Ania, Cyclobutanes in small-molecule drug candidates, *ChemMedChem*, 2022, **17**, e202200020.
- 2 T. T. Wager, B. A. Pettersen, A. W. Schmidt, D. K. Spracklin, S. Mente, T. W. Butler, H. J. Howard, D. J. Lettiere, D. M. Rubitski, D. F. Wong, F. M. Nedza, F. R. Nelson, H. Rollema, J. W. Raggon, J. Aubrecht, J. K. Freeman, J. M. Marcek, J. Cianfrogna, K. W. Cook, L. C. James, L. A. Chatman, P. A. Iredale, M. J. Banker, M. L. Homiski, J. B. Munzner and R. Y. Chandrasekaran, Discovery of two clinical histamine H3 receptor antagonists: *trans-N*-ethyl-3-fluoro-3-[3-fluoro-4-(pyrrolidinylmethyl)-phenyl]cyclobutanecarboxamide (PF-03654746) and *trans*-3-fluoro-3-[3-fluoro-4-(pyrrolidin-1-ylmethyl)phenyl]-*N*-(2-methylpropyl)cyclobutanecarboxamide (PF-03654764), *J. Med. Chem.*, 2011, **54**, 7602.
- 3 M. J. Mulvihill, A. Cooke, M. Rosenfeld-Franklin, E. Buck, K. Foreman, D. Landfair, M. O'Connor, C. Pirritt, Y. Sun, Y. Yao, L. D. Arnold, N. W. Gibson and Q.-S. Ji, Discovery of OSI-906 : a selective and orally efficacious dual inhibitor of the IGF-I receptor and insulin receptor, *Future Med. Chem.*, 2009, **1**, 1153.
- 4 K. Majima and M. Yamano, Diastereoselective synthesis of a *cis*-1,3-disubstituted cyclobutane carboxylic acid scaffold for TAK-828F, a potent retinoic acid receptor-related orphan receptor (ROR)- γ t inverse agonist, *J. Org. Chem.*, 2021, **86**, 11464.
- 5 For reviews on synthesis of cyclobutanes, see: (a) M. Wang and P. Lu, Catalytic approaches to assemble cyclobutane motifs in natural product synthesis, *Org. Chem. Front.*, 2018, **5**, 254; (b) E. N. Hancock, J. M. Wahl and M. K. Brown, Recent advances in the synthesis of gem-dimethylcyclobutane natural products, *Nat. Prod. Rep.*, 2019, **36**, 1383; (c) K.-G. Wen, Y.-Y. Peng and X.-P. Zeng, Advances in the catalytic asymmetric synthesis of quaternary carbon containing cyclobutanes, *Org. Chem. Front.*, 2020, **7**, 2576; (d) J. Li, K. Gao, M. Bian and H. Ding, Recent advances in the total synthesis of cyclobutane-containing natural products, *Org. Chem. Front.*, 2020, **7**, 136; (e) J. Chen, Q. Zhu, H. Fang and P. Lu, Dancing on ropes-enantioselective functionalization of preformed four-membered carbocycles, *Chin. J. Chem.*, 2022, **40**, 1346.
- 6 For representative examples on synthesis of 1,3-difunctionalized cyclobutanes by cycloadditions, see: (a) J. M. Hoyt, V. A. Schmidt, A. M. Tondreau and P. J. Chirik, Iron-catalyzed intermolecular [2+2] cycloadditions of unactivated alkenes, *Science*, 2015, **349**, 960; (b) M. L. Conner and M. K. Brown, Synthesis of 1,3-Substituted Cyclobutanes by Allenolate-Alkene [2+2] Cycloaddition, *J. Org. Chem.*, 2016, **81**, 8050; (c) J. M. Wahl, M. L. Conner and M. K. Brown, Allenolates in Enantioselective [2+2] Cycloadditions: From a Mechanistic Curiosity to a Stereospecific Transformation, *J. Am. Chem. Soc.*, 2018, **140**, 15943; (d) G. Li, A. K. Dilger, P. T. Cheng, W. R. Ewing and J. T. Groves, Selective C-H Halogenation with a Highly Fluorinated Manganese Porphyrin, *Angew. Chem., Int. Ed.*, 2018, **57**, 1251; (e) Z. Fan, D. A. Strassfeld, H. S. Park, K. Wu and J.-Q. Yu, Formal γ -C-H Functionalization of Cyclobutyl Ketones: Synthesis of *cis*-1,3-Difunctionalized Cyclobutanes, *Angew. Chem., Int. Ed.*, 2023, **62**, e202303948; (f) C. Zhong, Y. Huang, H. Zhang, Q. Zhou, Y. Liu and P. Lu, Enantioselective Synthesis of 3-Substituted Cyclobutenes by Catalytic Conjugate Addition/Trapping Strategies, *Angew. Chem., Int. Ed.*, 2020, **59**, 2750; (g) M. Yan, Q. Zhou and P. Lu, Collective synthesis of chiral tetrasubstituted cyclobutanes enabled by enantioconvergent Negishi cross-coupling of cyclobutenones, *Angew. Chem., Int. Ed.*, 2023, **62**, e202218008.
- 7 For synthesis of 1,1,3-trisubstituted cyclobutanes by ring openings of BCBs, see: (a) Y. Gaoni, Conjugate addition of organocopper reagents to 1-arylsulfonylbicyclobutanes synthesis of the racemic form of the six pheromone of the citrus mealybug, *Planococcus citri*(risso), *Tetrahedron Lett.*, 1982, **23**, 5215; (b) R. Panish, S. R. Chintala, D. T. Boruta, Y. Fang, M. T. Taylor and J. M. Fox, Enantioselective Synthesis of Cyclobutanes via Sequential Rh-catalyzed Bicyclobutanation/Cu-catalyzed Homoconjugate Addition, *J. Am. Chem. Soc.*, 2013, **135**, 9283; (c) R. A. Panish, S. R. Chintala and J. M. Fox, A Mixed-Ligand Chiral Rhodium(II) Catalyst Enables the Enantioselective Total Synthesis of Piperarborenine B, Radical Addition to Strained σ -Bonds Enables the Stereocontrolled Synthesis of Cyclobutyl Boronic Esters, *Angew. Chem., Int. Ed.*, 2016, **55**, 4983; (d) Y. Gaoni, A. Tomazic and E. Potgieter, Stereochemistry of addition of organocopper reagents and of the hydride ion to 1-(arylsulfonyl)bicyclo[1.1.0]butanes, *J. Org. Chem.*, 1985, **50**, 2943; (e) M. Silvi and V. K. Aggarwal, Radical Addition to Strained σ -Bonds Enables the Stereocontrolled Synthesis of Cyclobutyl Boronic Esters, *J. Am. Chem. Soc.*, 2019, **141**, 9511; (f) A. Fawcett, T. Biberger and V. K. Aggarwal, Carbopalladation of C-C σ -bonds enabled by strained boronate complexes, *Nat. Chem.*, 2019, **11**, 117; (g) S. H. Bennett, A. Fawcett, E. H. Denton, T. Biberger, V. Fasano, N. Winter and V. K. Aggarwal, Difunctionalization of C-C σ -Bonds Enabled by the Reaction of Bicyclo[1.1.0]butyl Boronate Complexes with Electrophiles: Reaction Development, Scope, and Stereochemical Origins, *J. Am. Chem. Soc.*, 2020, **142**, 16766; (h) B. Wöfl, N. Winter, J. Li, A. Noble and V. K. Aggarwal, Strain-Release Driven Epoxidation and Aziridination of Bicyclo[1.1.0]butanes via Palladium Catalyzed σ -Bond Nucleopalladation, *Angew. Chem., Int. Ed.*, 2023, **62**, e202217064; (i) F. W. Goetzke, A. M. L. Hell, L. van Dijk and S. P. Fletcher, A catalytic asymmetric cross-coupling approach to the synthesis of cyclobutanes, *Nat. Chem.*, 2021, **13**, 880; (j) D. Egea-Arrebola, F. W. Goetzke and S. P. Fletcher, Rhodium-Catalyzed Asymmetric



- Arylation of Cyclobutenone Ketals, *Angew. Chem., Int. Ed.*, 2023, **62**, e202217381; (k) M. Takatsuki, H. Aoyama, K. Murai, M. Arisawa and M. Sako, Heteroannulation of bicyclobutane derivatives via Au-catalyzed hydration to enol ethers and intramolecular cyclization giving spirocyclobutanes, *Chem. Commun.*, 2023, **59**, 7467.
- 8 (a) M. Golfmann and J. C. L. Walker, Bicyclobutanes as unusual building blocks for complexity generation in organic synthesis, *Commun. Chem.*, 2023, **6**, 9; (b) C. B. Kelly, J. A. Milligan, L. J. Tilley and T. M. Sodano, Bicyclobutanes: from curiosities to versatile reagents and covalent warheads, *Chem. Sci.*, 2022, **13**, 11721; (c) A. Fawcett, Recent advances in the chemistry of bicycle- and 1-azabicyclo[1.1.0]butanes, *Pure Appl. Chem.*, 2020, **92**, 751; (d) M. A. A. Walczak, T. Krainz and P. Wipf, Ring-Strain-Enabled Reaction Discovery: New Heterocycles from Bicyclo[1.1.0]butanes, *Acc. Chem. Res.*, 2015, **48**, 1149.
- 9 (a) H. K. Hall Jr and A. B. Padias, Bicyclobutanes and Cyclobutenes: Unusual Carbocyclic Monomers, *J. Polym. Sci., Part A: Polym. Chem.*, 2003, **41**, 62; (b) A. M. Dilmaç, E. Spuling, A. de Meijere and S. Bräse, Propellanes-From a Chemical Curiosity to “Explosive” Materials and Natural Products, *Angew. Chem., Int. Ed.*, 2017, **56**, 5684.
- 10 A. Kaur, W. Lin, V. Dovhalyuk, L. Driutti, M. L. D. Martino, M. Vujasinovic, J.-M. Löhr, M. E. Sellin and D. Globisch, Chemoselective bicyclobutane-based mass spectrometric detection of biological thiols uncovers human and bacterial metabolites, *Chem. Sci.*, 2023, **14**, 5291.
- 11 P. Zhang, R. Zhuang, X. Wang, H. Liu, J. Li, X. Su, X. Chen and X. Zhang, Highly Efficient and Stable Strain-Release Radioiodination for Thiol Chemoselective Bioconjugation, *Bioconjugate Chem.*, 2018, **29**, 467.
- 12 K. B. Wiberg, G. M. Lampman, R. P. Ciula, D. S. Connor, P. Schertler and J. Lavanish, Bicyclo[1.1.0]butane, *Tetrahedron*, 1965, **21**, 2749.
- 13 (a) P. Wipf and M. A. A. Walczak, Pericyclic cascade reactions of (bicyclo-[1.1.0]butylmethyl)amines, *Angew. Chem., Int. Ed.*, 2006, **45**, 4172; (b) M. A. A. Walczak and P. Wipf, Rhodium(I)-Catalyzed Cycloisomerizations of Bicyclobutanes, *J. Am. Chem. Soc.*, 2008, **130**, 6924; (c) R. Kleinmans, T. Pinkert, S. Dutta, T. O. Paulisch, H. Keum, C. G. Daniliuc and F. Glorius, Intermolecular $[2\pi+2\sigma]$ -photocycloaddition enabled by triplet energy transfer, *Nature*, 2022, **605**, 477; (d) Y. Liang, R. Kleinmans, C. G. Daniliuc and F. Glorius, Synthesis of polysubstituted 2-oxabicyclo[2.1.1]hexanes via visible-light-induced energy transfer, *J. Am. Chem. Soc.*, 2022, **144**, 20207; (e) Y. Liang, F. Paulus, C. G. Daniliuc and F. Glorius, Catalytic formal $[2\pi+2\sigma]$ cycloaddition of aldehydes with bicyclobutanes: expedient access to polysubstituted 2-oxabicyclo[2.1.1]hexanes, *Angew. Chem., Int. Ed.*, 2023, **62**, e202305043; (f) R. Guo, Y.-C. Chang, L. Herter, C. Salome, S. E. Braley, T. C. Fessard and M. K. Brown, Strain-release $[2\pi+2\sigma]$ cycloadditions for the synthesis of bicyclo[2.1.1]hexanes initiated by energy transfer, *J. Am. Chem. Soc.*, 2022, **144**, 7988; (g) Y. Zheng, W. Huang, R. K. Dhungana, A. Granados, S. Keess, M. Makvandi and G. A. Molander, Photochemical intermolecular $[3\sigma+2\sigma]$ -cycloaddition for the construction of aminobicyclo[3.1.1]heptanes, *J. Am. Chem. Soc.*, 2022, **144**, 23685; (h) S. Agasti, F. Beltran, E. Pye, N. Kaltsoyannis, G. E. M. Crisenza and D. J. Procter, A catalytic alkene insertion approach to bicyclo[2.1.1]hexane bioisosteres, *Nat. Chem.*, 2023, **15**, 535; (i) T. Yu, J. Yang, Z. Wang, Z. Ding, M. Xu, J. Wen, L. Xu and P. Li, Selective $[2\sigma+2\sigma]$ cycloaddition enabled by boronyl radical catalysis: synthesis of highly substituted bicyclo[3.1.1]heptanes, *J. Am. Chem. Soc.*, 2023, **145**, 4304; (j) M. Xu, Z. Wang, Z. Sun, Y. Ouyang, Z. Ding, T. Yu, L. Xu and P. Li, Diboron(4)-catalyzed remote $[3+2]$ cycloaddition of cyclopropanes via dearomative/rearomative radical transmission through pyridine, *Angew. Chem., Int. Ed.*, 2022, **61**, e202214507; (k) Y. Liu, S. Lin, Y. Li, J.-H. Xue, Q. Li and H. Wang, Pyridine-boryl radical-catalyzed $[2\pi+2\sigma]$ cycloaddition of bicyclo[1.1.0]butanes with alkenes, *ACS Catal.*, 2023, **13**, 5096.
- 14 For addition of carbon-centered radicals, see: (a) X. Wu, W. Hao, K.-Y. Ye, B. Jiang, G. Pombar, Z. Song and S. Lin, Ti-catalyzed radical alkylation of secondary and tertiary alkyl chlorides using Michael acceptors, *J. Am. Chem. Soc.*, 2018, **140**, 14836; (b) G. Ernouf, E. Chirkin, L. Rhyman, P. Ramasami and J.-C. Cintrat, Photochemical strain-release-driven cyclobutylolation of C(sp³)-centered radicals, *Angew. Chem., Int. Ed.*, 2020, **59**, 2618; (c) C. J. Pratt, R. A. Aycock, M. D. King and N. T. Jui, Radical α -C-H cyclobutylolation of aniline derivatives, *Synlett*, 2020, **31**, 51; (d) H. Gao, L. Guo, C. Shi, Y. Zhu, C. Yang and W. Xia, Transition metal-free radical α -oxy C-H cyclobutylolation via photoinduced hydrogen atom transfer, *Adv. Synth. Catal.*, 2022, **364**, 2140.
- 15 (a) S. Hoz, C. Azran and A. Sella, Atomic motions and protonation stereochemistry in nucleophilic additions to bicyclobutanes, *J. Am. Chem. Soc.*, 1996, **118**, 5456; (b) L. Guo, A. Noble and V. K. Aggarwal, α -Selective ring-opening reactions of bicyclo[1.1.0]butyl boronic ester with nucleophiles, *Angew. Chem., Int. Ed.*, 2021, **60**, 212; (c) Y. Gaoni, Regiospecific additions of hydrazoic acid and benzylamine to 1-(arylsulfonyl)bicyclo[1.1.0]butanes. application to the synthesis of *cis* and *trans* 2,7-methanoglutamic acids, *Tetrahedron Lett.*, 1988, **29**, 1591; (d) R. Gianatassio, J. M. Lopchuk, J. Wang, C.-M. Pan, L. R. Malins, L. Prieto, T. A. Brandt, M. R. Collins, G. M. Gallego, N. W. Sach, J. E. Spangler, H. Zhu, J. Zhu and P. S. Baran, Strain-release amination, *Science*, 2016, **351**, 241; (e) J. A. Milligan, C. A. Busacca, C. H. Senanayake and P. Wipf, Hydrophosphination of bicyclo[1.1.0]butane-1-carbonitriles, *Org. Lett.*, 2016, **18**, 4300; (f) Y. Gaoni, New bridgehead-substituted 1-(arylsulfonyl)bicyclo[1.1.0]butanes and some novel addition reactions of the bicyclic system, *Tetrahedron*, 1989, **45**, 2819.
- 16 Z. Zhang and V. Gevorgyan, Palladium hydride-enabled hydroalkenylation of strained molecules, *J. Am. Chem. Soc.*, 2022, **144**, 20875.
- 17 M. Ociepa, A. J. Wierzba, J. Turkowska and D. Gryko, Polarity-reversal strategy for the functionalization of



- electrophilic strained molecules *via* light-driven cobalt catalysis, *J. Am. Chem. Soc.*, 2020, **142**, 5355.
- 18 K. Dhake, K. J. Woelk, J. Becica, A. Un, S. E. Jenny and D. C. Leitch, Beyond bioisosteres: divergent synthesis of azabicyclohexanes and cyclobutenyl amines from bicyclobutanes, *Angew. Chem., Int. Ed.*, 2022, **61**, e202204719.
- 19 During the preparation of our manuscript, an elegant study describing Bi(OTf)₃-catalyzed ring-opening of BCBs with naphthols was reported: A. Guin, S. Bhattacharjee, M. S. Harariya and A. T. Biju, Lewis acid-catalyzed diastereoselective carbonyl functionalization of bicyclobutanes employing naphthols, *Chem. Sci.*, 2023, **14**, 6585.
- 20 (a) L. A. Paquette, R. P. Henzel and S. E. Wilson, The influence of structural features on the course of bicyclo [1.1.0]butane rearrangements catalysed by silver (I) ion, *J. Am. Chem. Soc.*, 1972, **94**, 7780; (b) L. A. Paquette, S. E. Wilson and R. P. Henzel, Mechanistic aspects of the silver(I)-promoted rearrangements of tricyclo [4.1.0.0] heptane derivatives. Deuterium isotope effect studies and independent generation of argento carbonium ions, *J. Am. Chem. Soc.*, 1972, **94**, 7771; (c) M. Sakai, H. H. Westberg, H. Yamaguchi and S. Masamune, Silver(I)-catalyzed rearrangement of bicyclobutanes. Some aspects of the mechanism II, *J. Am. Chem. Soc.*, 1971, **93**, 4611; (d) L. A. Paquette, Catalysis of strained σ -bond rearrangements by silver(I) ion, *Acc. Chem. Res.*, 1971, **4**, 280; (e) K. C. Bishop III, Transition metal catalyzed rearrangements of small ring organic molecules, *Chem. Rev.*, 1976, **76**, 461; (f) R. K. Kumar and X. Bi, Catalytic σ -activation of carbon-carbon triple bonds: reactions of propargylic alcohols and alkynes, *Chem. Commun.*, 2016, **52**, 853; (g) M. Li, W. Wu and H. Jiang, Recent advances in silver-catalyzed transformations of electronically unbiased alkenes and alkynes, *ChemCatChem*, 2020, **12**, 5034; (h) Q.-Z. Zheng and N. Jiao, Ag-catalyzed C-H/C-C bond functionalization, *Chem. Soc. Rev.*, 2016, **45**, 4590; (i) J.-Y. Son, S. Aikonen, N. Morgan, A. S. Harmata, J. J. Sabatini, R. C. Sausa, E. F. C. Byrd, D. H. Ess, R. S. Paton and C. R. J. Stephenson, Exploring Cuneanes as Potential Benzene Isosteres and Energetic Materials: Scope and Mechanistic Investigations into Regioselective Rearrangements from Cubanes, *J. Am. Chem. Soc.*, 2023, **145**, 16355; (j) E. Smith, K. D. Jones, L. O'Brien, S. P. Argent, C. Salome, Q. Lefebvre, A. Valery, M. Böcü, G. N. Newton and H. W. Lam, Silver(I)-Catalyzed Synthesis of Cuneanes from Cubanes and their Investigation as Isosteres, *J. Am. Chem. Soc.*, 2023, **145**, 16365; (k) H. Takebe and S. Matsubara, Catalytic Asymmetric Synthesis of 2,6-Disubstituted Cuneanes through Enantioselective Constitutional Isomerization of 1,4-Disubstituted Cubanes, *Eur. J. Org. Chem.*, 2022, e202200567.
- 21 (a) T.-Y. Lin, C.-Z. Zhu, P. Zhang, Y. Wang, H.-H. Wu, J.-J. Feng and J. Zhang, Regiodivergent intermolecular [3+2] cycloadditions of vinyl aziridines and allenes: stereospecific synthesis of chiral pyrrolidines, *Angew. Chem., Int. Ed.*, 2016, **55**, 10844; (b) C.-Z. Zhu, J.-J. Feng and J. Zhang, Rhodium(I)-catalyzed intermolecular aza-[4+3] cycloaddition of vinyl aziridines and dienes: atom-economical synthesis of enantiomerically enriched functionalized azepines, *Angew. Chem., Int. Ed.*, 2017, **56**, 1351; (c) T.-Y. Lin, H.-H. Wu, J.-J. Feng and J. Zhang, Transfer of chirality in the rhodium-catalyzed chemoselective and regioselective allylic alkylation of hydroxyarenes with vinyl aziridines, *Org. Lett.*, 2017, **19**, 2897.
- 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.†
- 23 DFT calculations were performed by using the Gaussian 16 package under the level of B3LYP-D3(BJ)/def2-TZVP-SMD(toluene)//B3LYP-D3(BJ)/6-31G(d,p) and SDD for the Ag atom. See the ESI† for computational details.

