JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
pubs.acs.org/JACS
Communication

Enantioselective Synthesis of Chiral Cyclobutenes Enabled by Brønsted Acid-Catalyzed Isomerization of BCBs

Si-Li Lin, Ye-Hui Chen,* Huan-Huan Liu, Shao-Hua Xiang, and Bin Tan*

Cite This: J. Am. Chem. Soc. 2023, 145, 21152−21158
Read Online
ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: Chiral cyclobutene units are commonly found in natural products and biologically active molecules. Transition-metal-catalysis has been extensively used in asymmetric synthesis of such structures, while organocatalytic approaches remain elusive. In this study, bicyclo[1.1.0]butanes are involved in enantioselective transformation for the first time to offer a highly efficient route toward cyclobutenes with good regio- and enantiocontrol. The utilization of *N*-triflyl phosphoramide as a chiral Brønsted acid promoter enables this isomerization process to proceed under mild conditions with low catalyst loading as well as good functional group compatibility. The resulting chiral cyclobutenes could serve as platform molecules for downstream manipulations with excellent reservation of stereochemical integrity, demonstrating the synthetic practicality of the developed method. Control experiments have also been performed to verify the formation of a key carbocation intermediate at the benzylic position.

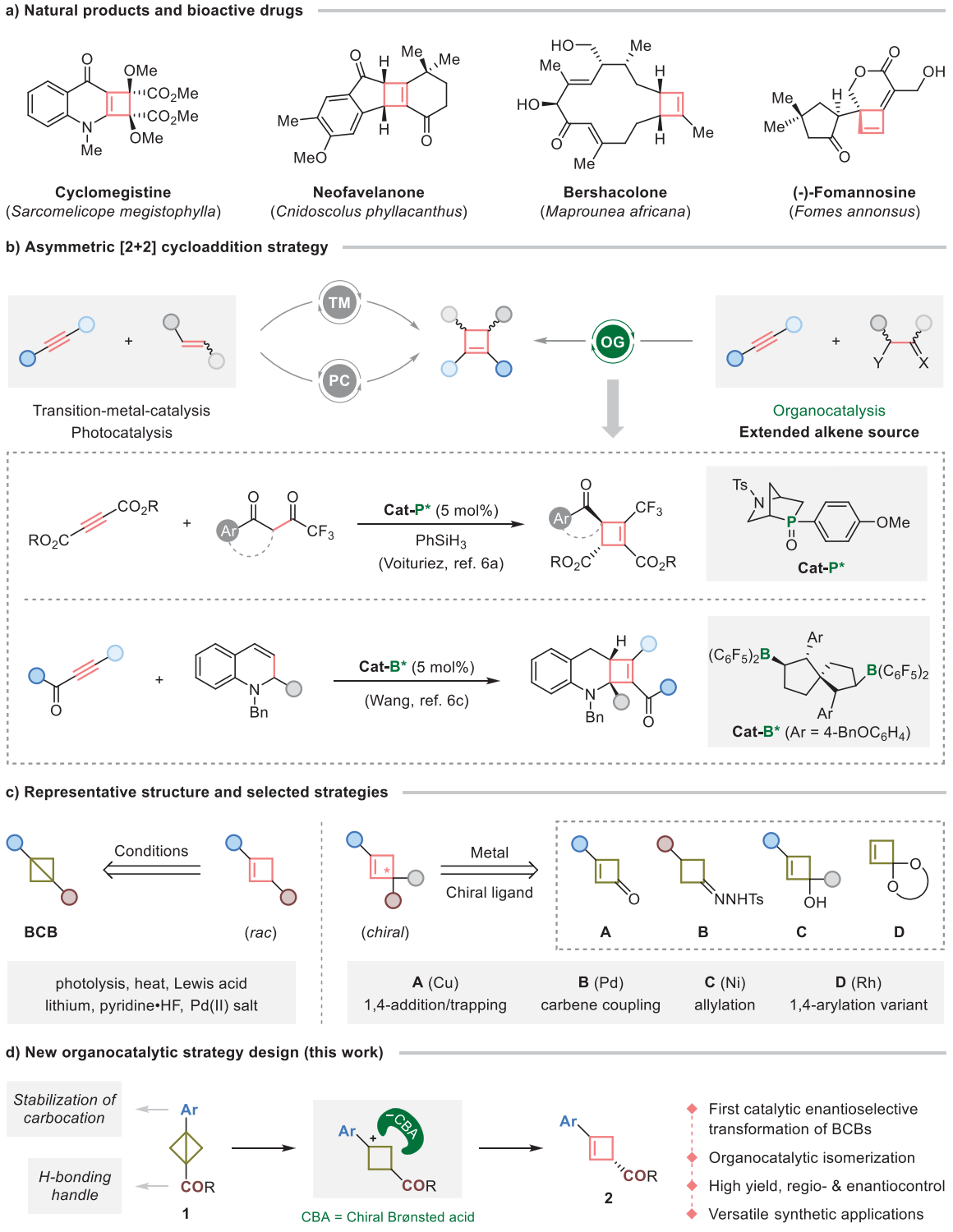
Chiral cyclobutene units are prevalent in natural products and biologically relevant molecules (Scheme 1a).[1] The featured ring strain and double bond handle render them as versatile chiral building blocks for a series of downstream manipulations.[2] Accordingly, enantioselective assembly of these core structures has attracted much attention from the synthetic community and various catalytic asymmetric strategies have been elegantly established over the past few decades.[3] Among these achievements, transition metal catalytic [2 + 2] cycloaddition between alkynes and alkenes has been recognized as one of the most successful methods.[3a,k] This tactic has also been attempted by means of photoredox catalysis, however the enantiocontrol remains challenging for most of the substrates.[4] Given the unique activation mode as well as the verified stereoinduction capability, organocatalysis[5] has effectively enabled the extension of the alkene source for the [2 + 2] cycloaddition reaction with alkynes. For instance, 1,3-dione structures were successfully utilized in this type of transformation by Voituriez's group exploiting $P^{III}/P^{V}{=}O$ redox catalytic cycling,[6a,b] while Wang and co-workers reported a Lewis acidic chiral-borane-catalytic regio- and enantioselective [2 + 2] cycloaddition of alkynones and 1,4-dihydroquinolines starting from their double bond shift isomers 1,2-dihydroquinolines (Scheme 1b).[6c] Nevertheless, the application of organocatalysis in enantioselective synthesis of chiral cyclobutenes remains in its infancy as compared to transition metal catalysis, and the development of more practical strategies involving other types of substrates is still highly desirable.

On the other hand, bicyclo[1.1.0]butanes (BCBs), as the smallest fused hydrocarbon rings, have abundant synthetic value due to high strain energy.[7] They have participated in a wide array of transformations through rapid C−C bond cleavage,[8] which offered a straightforward route to access numerous significant frameworks, particularly spirocycles and bridged bicycloalkanes.[9] More importantly, cyclobutene structures could also be forged from BCBs via treatment with photolysis,[10] heat,[11] lithium,[12] pyridine·HF,[13] Pd(II) salts,[14] or Lewis acids.[11] However, they are always recorded as byproducts or in situ generated intermediates, and low chemical yields are provided for most cases. For the asymmetric assembly of such a type of structures, significant accomplishments have been gained by means of transition-metal-catalysis with cyclobutenones,[15a] cyclobutanone-derived *N*-sulfonylhydrazones,[15b] cyclobutenols[15c] or cyclobutenone ketals[15d] as the starting materials. Nonetheless, BCBs have been scarcely involved in asymmetric transformations, and the enantiocontrol for the isomerization process of BCBs to cyclobutenes, to the best of our knowledge, has been never challenged. The pioneering findings incorporating our understanding in organocatalysis inspired us to conquer this transformation with a chiral Brønsted acid (CBA).[16] The decisive factor of the present scenario belongs to the selection of suitable BCB substrates and a CBA catalyst. In our design, a carbonyl group which could function as a hydrogen-bond activation handle for CBA is installed at the bridgehead of BCB **1**, while an aromatic substituent is posited at the other bridgehead to stabilize the potentially formed carbocation intermediate. This design would also enhance the control of regioselectivity and improve the yield of desired product **2**. For CBA, it should possess sufficient acidity to promote the protonation course, besides its conventional role in the dictation of stereochemistry. Herein, we disclose the first asymmetric transformation of BCBs **1** enabled by a highly

Received: June 20, 2023
Published: September 21, 2023

https://doi.org/10.1021/jacs.3c06525
J. Am. Chem. Soc. 2023, 145, 21152−21158

Scheme 1. Significance of Chiral Cyclobutene Structures and Representative Catalytic Enantioselective Construction Approaches

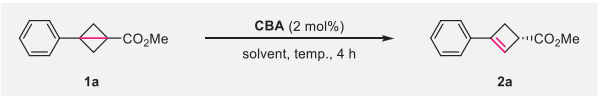


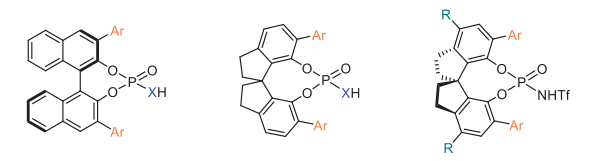
acidic *N*-triflyl phosphoramide catalyst,[17] offering a novel and practical approach to furnish cyclobutenes **2** in a highly regio- and enantioselective manner (Scheme 1c).

Based on the design, our initial investigation on this enantioselective isomerization commenced with BCB **1a** as the model substrate. The reaction was performed in CH_2Cl_2 at room temperature and, unsurprisingly, BINOL-derived chiral phosphoric acid (*R*)-**C1** afforded the isomerized product **2a** in low conversion and nearly without enantiocontrol after 4 h (Table 1, entry 1). The prolongation of the reaction duration brought about no visible improvement in the outcome. Delightfully, the yield was boosted to more than 90% when more acidic *N*-triflyl phosphoramide (*R*)-**C2** or (*R*)-**C3** was utilized, albeit with low *ee* values (entries 2 and 3). Next, the effect of the axially chiral skeleton on CBA was evaluated. Poor results remained for SPINOL-derived chiral phosphoric acids

https://doi.org/10.1021/jacs.3c06525
J. Am. Chem. Soc. 2023, 145, 21152−21158

Table 1. Reaction Condition Optimization for Enantioselective Synthesis of Chiral Cyclobutene[a]





(*R*)-**C1**, X = O, Ar = 2-naphthyl
(*R*)-**C2**, X = NTf, Ar = 9-anthracenyl
(*R*)-**C3**, X = NTf, Ar = 1-pyrenyl
(*R*)-**C4**, X = O, Ar = 1-pyrenyl
(*R*)-**C5**, X = O, Ar = 3,5-*t*Bu$_2$-C$_6$H$_3$
(*S*)-**C6**, X = NTf, Ar = 1-pyrenyl
(*S*)-**C7**, R = Br, Ar = 1-pyrenyl
(*S*)-**C8**, R = Me, Ar = 1-pyrenyl
(*S*)-**C9**, R = Me, Ar = 9-phenanthryl

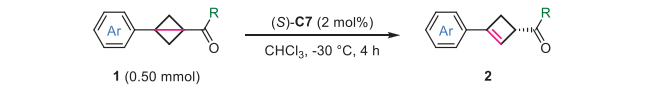
entry	CBA	solvent	temp.	yield (%)	*ee* (%)
1	(*R*)-**C1**	CH_2Cl_2	r.t.	25	6
2	(*R*)-**C2**	CH_2Cl_2	r.t.	90	26
3	(*R*)-**C3**	CH_2Cl_2	r.t.	93	25
4	(*R*)-**C4**	CH_2Cl_2	r.t.	21	1
5	(*R*)-**C5**	CH_2Cl_2	r.t.	28	7
6	(*S*)-**C6**	CH_2Cl_2	r.t.	95	69
7	(*S*)-**C7**	CH_2Cl_2	r.t.	95	70
8	(*S*)-**C8**	CH_2Cl_2	r.t.	94	65
9	(*S*)-**C9**	CH_2Cl_2	r.t.	96	62
10	(*S*)-**C7**	CH_2Cl_2	−15 °C	95	83
11	(*S*)-**C7**	CH_2Cl_2	−25 °C	96	86
12	(*S*)-**C7**	CH_2Cl_2	−30 °C	95	87
13	(*S*)-**C7**	CH_2Cl_2	−40 °C	95	86
14	**(*S*)-C7**	**$CHCl_3$**	**−30 °C**	**98 (95)**[b]	**90 (90)**[b]
15	(*S*)-**C7**	DCE	−30 °C	89	83

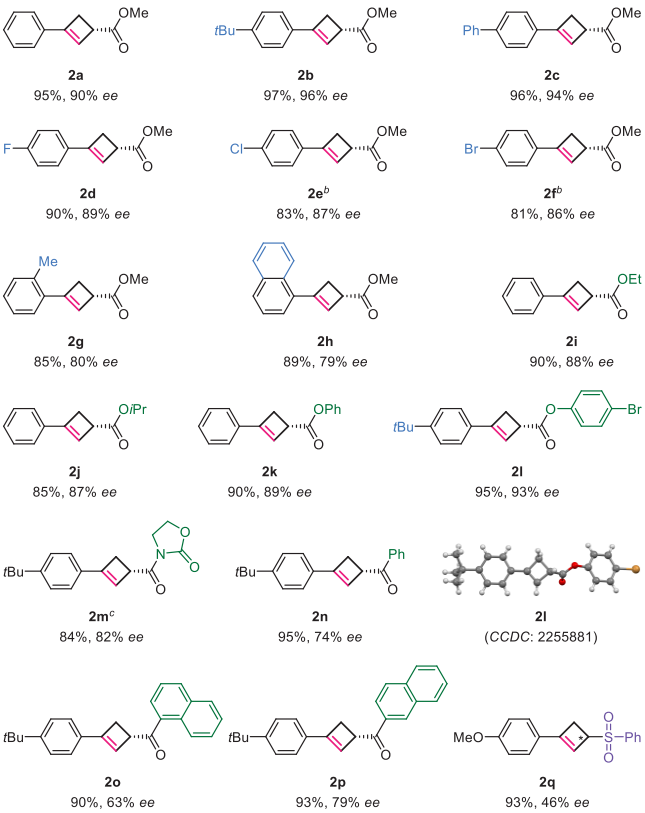
[a]Reaction conditions: **1a** (0.05 mmol), CBA (2 mol %) in solvent (1 mL) at noted temperature for 4 h. Isolated yield was provided and *ee* values were determined by chiral HPLC. [b]Reaction scale: 0.50 mmol.

(*R*)-**C4** or (*R*)-**C5** (entries 4 and 5), while *N*-triflyl phosphoramide (*S*)-**C6** harboring a 1-pyrenyl substitution at 6,6′-positions gave a meaningful increase of enantiocontrol and maintained excellent yield (entry 6). The introduction of substituent at 4,4′-positions of the SPINOL backbone led to inapparent influence (entries 7−9) and bromo-substituted (*S*)-**C7** was found to afford the best enantioinduction (entry 8). Following studies revealed that improved enantioselectivity could be achieved through decreasing temperature, and meanwhile, no deterioration of efficiency was observed (entries 10−13). The screening of solvent at −30 °C (entries 14 and 15) identified the superiority of $CHCl_3$ and provided chiral cyclobutene **2a** with 90% enantiopurity. The excellent results could be perfectly preserved when the reaction was conducted on a 0.50 mmol scale (entry 14).

After the establishment of the optimal conditions, the substrate generality of this CBA catalyzed enantioselective isomerization reaction from BCBs **1** to chiral cyclobutenes **2** was investigated. Representative examples are displayed in Table 2. First, the effect for the substituent on the phenyl ring was tested. The installation of an electron-donating *tert*-butyl group at the *para*-position could improve the enantioselectivity and retain excellent yield (**2b**). A phenyl substituted substrate gave the 0-bridge bond cleavage product **2c** in 96% yield with 94% enantiopurity. When an electron-withdrawing halogen atom was equipped, both the yield and enantiocontrol were dropped, even with a prolonged reaction duration (**2d**−**2f**). Methyl substituent orientated at the *ortho*-site led to an adverse

Table 2. Substrate Generality of Chiral Cyclobutenes[a]





[a]Reaction conditions: unless otherwise stated, reaction of **1** (0.5 mmol) with (*S*)-**C7** (2 mol %) was carried out in $CHCl_3$ (10 mL) at −30 °C for 4 h. Isolated yield was provided for **2** and *ee* values were determined by chiral HPLC. [b]Reaction duration: 6 h. [c]CH_2Cl_2 (0.05 M).

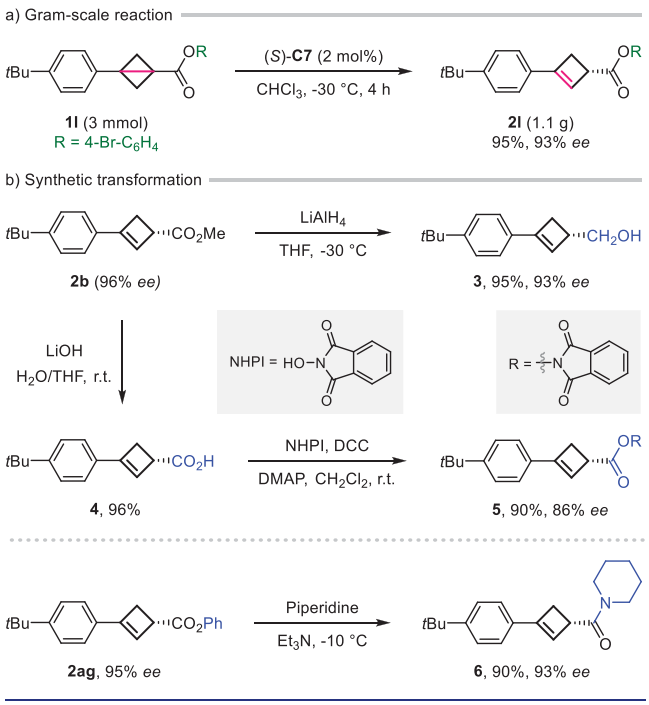
effect on this reaction (**2g**). Naphthyl-substituted BCB was also an applicable candidate to give the desired product **2h** in 89% yield with 79% ee. However, BCBs bearing a strong electron-withdrawing group exerted limited reactivity, which may be ascribed to the low stability of the formed carbonation intermediate. For instance, *para*-trifluoromethyl decorated BCB afforded only a trace amount of target product under standard conditions. Next, the influence of the ester substituent at the bridgehead of BCB was evaluated. All explored aliphatic and aromatic esters were found to be compatible with this catalytic system well, furnishing the corresponding products **2i**−**2k** in 87−89% enantiopurities. Given the superior result of BCBs that bear a *tert*-butyl at the *para*-position of the phenyl group (**2b**), further extension of the substrate generality was implemented with this best-performing aromatic substituent. Expectedly, BCB with aromatic ester was tolerated to give **2l** with remarkable efficiency and enantiocontrol. Apart from the ester, imide functionalized BCBs were also smoothly isomerized to the corresponding products **2m** in 84% yield with 82% enantiopurity. Furthermore, aromatic ketone substituted BCBs were efficiently converted under the standard conditions, albeit with significantly deteriorated enantioselectivities (**2n**−**2p**). For sulfonyl decorated BCBs, the introduction of a

https://doi.org/10.1021/jacs.3c06525
J. Am. Chem. Soc. 2023, 145, 21152−21158

methoxy at the *para*-site of phenyl could provide **2q** in 93% yield with an *ee* value of 46%, while the electron-withdrawing substituent such as a cyano or ester group resulted in complete inhibition of C−C bond cleavage. Similarly, BCB with a methyl substitution rather than an aromatic ring was recovered under the developed conditions (for more details, see Supplementary Table S4). Additional BCB substrates that were successfully utilized in this process are included in Supplementary Table S3. The absolute configuration of **2l** was determined by X-ray diffraction analysis (CCDC 2255881) and the stereochemistry of other products was assigned by analogy.

To verify the synthetic utility of the developed method, a gram-scale synthesis of chiral cyclobutene **2l** was performed. As shown in Scheme 2a, the remarkable outcome was

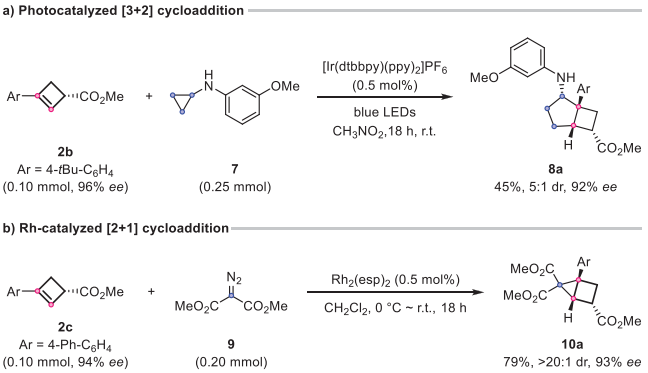
Scheme 2. Gram-Scale Synthesis of Chiral Cyclobutene and Transformations



completely maintained, paving a practical way for large-scale production. Subsequently, synthetic transformations of the generated products were demonstrated (Scheme 2b). First, the reduction of **2b** with $LiAlH_4$ gave alcohol **3** in 95% yield with a slight erosion of the stereochemical integrity. Upon hydrolysis with lithium hydroxide (LiOH), compound **2b** was rapidly transformed into carboxylic acid **4**, which was then treated with *N*-hydroxyphthalimide (NHPI) to afford redox-active ester **5** in a satisfactory yield. However, the enantiopurity decreased by 10% throughout this two-step process. In addition, the amidation of **2ag** with piperidine afforded chiral cyclobutene **6** in 90% yield with an excellent retention of *ee*.

Furthermore, application of the obtained highly enantioenriched cyclobutenes as platform molecules for transformation to complex three-dimensional frameworks was attempted. Capitalizing on the C=C bond handle, [3 + 2] cycloaddition of cyclobutenes with cyclopropylamine **7** was surveyed by means of photoredox catalysis.[18] As displayed in Scheme 3a, cyclobutene **2b** was successfully converted to functionalized bicyclo[3.2.0]heptane **8a** in moderate yields and diastereocontrol. To our delight, the stereochemical integrity was perfectly

Scheme 3. Application as Platform Molecules in Cycloaddition Reactions



preserved. Moreover, [2 + 1] cycloaddition reaction of **2c** with diazoester **9** also proceeded well under rhodium catalysis[14] to afford highly enantioenriched bicyclo[2.1.0]pentane **10a** in 79% yield with excellent diastereoselectivity (Scheme 3b). More investigated examples are summarized in Supplementary Tables S6 and S7.

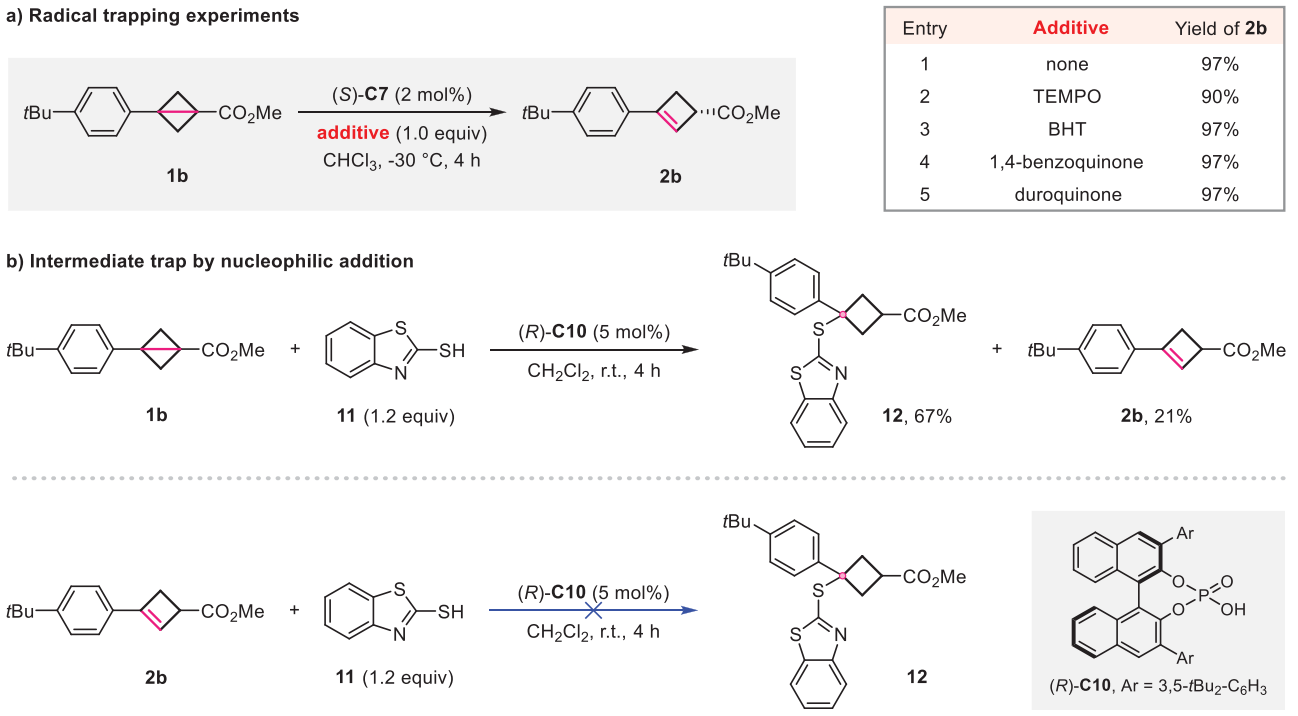
To probe the reaction mechanism, a series of control experiments were conducted. First, several conventionally used free radical scavengers were included for the reactions with **1b** as model substrate and all these reactions afforded **2b** in more than 90% yield under the standard conditions, thus ruling out a radical pathway (Scheme 4a). Subsequently, 2-benzothiazolethiol **11** was introduced to trap the carbocation intermediate.[19] However, we did not detect any nucleophilic addition product **12** under the developed conditions due to the high catalytic activity of (*S*)-**C7**. Therefore, a weaker acidic catalyst (*R*)-**C10** was attempted and this reaction could successfully produce **12** in 67% yield, along with the isolation of cyclobutene **2b** in 21% yield. In contrast, treatment of **2b** with **11** failed to give adduct **12** (Scheme 4b). These results suggest that a stabilized carbocation intermediate is formed during the isomerization process.

To elucidate the transition state of this process, a Hammett analysis[20] was conducted with different *para*-substituents on aryl group of BCBs (Scheme 4c). A negative linear correlation was observed through plotting $\log(k_X/k_H)$ against σ_p^+. The observed linear free-energy relationship ($\rho^+ = -2.67 \pm 0.19$) further manifested the existence of the positive charge at the benzylic site during the isomerization process. Based on the above experimental results, a plausible mechanism was proposed in Scheme 4d.[21] Initially, BCB **1** is activated by *N*-triflyl phosphoramide, which generates **Int A** through the formation of a hydrogen bond. Subsequently, the cleavage of the 0-bridge bond leads to the formation of an ion pair, **Int B**, which can then convert to **Int C** via enolate-to-ketone tautomerization involving the transfer of a hydrogen atom to the adjacent carbon atom. Finally, deprotonation occurs under the influence of the *N*-triflyl phosphoramide anion, leading to the formation of cyclobutene **2** and the regeneration of the acid catalyst.

In summary, we have realized the first catalytic asymmetric transformation of BCBs by means of organocatalysis to offer a rapid route for synthesizing highly enantioenriched cyclobutene structures. The asymmetric isomerization process displays several features, including mild reaction conditions, low catalyst loading, as well as compatibility with a wide range of BCB substrates. *N*-Triflyl phosphoramide was employed in

https://doi.org/10.1021/jacs.3c06525
J. Am. Chem. Soc. 2023, 145, 21152−21158

Scheme 4. Mechanistic Investigations and Proposed Reaction Pathway



this study due to its high catalytic activity and enantiocontrol ability. The synthetic practicality of this method is demonstrated by the successful involvement of the resulting cyclobutenes in [3 + 2] and [2 + 1] cycloaddition reactions with excellent reservation of stereochemical integrity. Additionally, our experimental analyses support a plausible mechanism concerning the activation of BCB by the acid catalyst, followed by a key ion pair intermediate leading to the formation of the chiral cyclobutene product. The applications of both BCBs and chiral cyclobutenes in asymmetric synthesis are currently being explored.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.3c06525.

Experimental procedures, characterization data of new compounds, copies of ^{1}H NMR, ^{13}C NMR spectra and HPLC profiles (PDF)

Accession Codes

CCDC 2255881 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Authors

Ye-Hui Chen − *Shenzhen Grubbs Institute, Department of Chemistry, Southern University of Science and Technology, Shenzhen 518055, China*; Email: chenyh@sustech.edu.cn

https://doi.org/10.1021/jacs.3c06525
J. Am. Chem. Soc. 2023, 145, 21152−21158

Bin Tan − *Shenzhen Grubbs Institute, Department of Chemistry, Southern University of Science and Technology, Shenzhen 518055, China;* orcid.org/0000-0001-8219-9970; Email: tanb@sustech.edu.cn

Authors

Si-Li Lin − *Shenzhen Grubbs Institute, Department of Chemistry, Southern University of Science and Technology, Shenzhen 518055, China*

Huan-Huan Liu − *Shenzhen Grubbs Institute, Department of Chemistry, Southern University of Science and Technology, Shenzhen 518055, China*

Shao-Hua Xiang − *Shenzhen Grubbs Institute, Department of Chemistry, Southern University of Science and Technology, Shenzhen 518055, China; Academy for Advanced Interdisciplinary Studies, Southern University of Science and Technology, Shenzhen 518055, China;* orcid.org/0000-0003-4262-5626

Complete contact information is available at: https://pubs.acs.org/10.1021/jacs.3c06525

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful for financial support from the National Key R&D Program of China (2022YFA1503703, 2021YFF0701604), the National Natural Science Foundation of China (21825105, 22231004, 22271135), Guangdong Innovative Program (2019BT02Y335), and Shenzhen Science and Technology Program (KQTD20210811090112004, JCYJ20210324120205016, JCYJ20210324105005015). The authors appreciate the assistance of SUSTech Core Research Facilities.

■ REFERENCES

(1) (a) Endo, Y.; Ohta, T.; Nozoe, S. Neofavelanone, A Novel Tetracyclic Cyclobutene Derivative from the Brazilian Plant, *Cnidoscolus Phyllacanthus*. *Tetrahedron Lett.* **1992**, *33*, 353−356. (b) Bernart, M. W.; Kashman, Y.; Tischler, M.; Cardellina, J. H.; Boyd, M. R. Bershacolone, an Unprecedented Diterpene Cyclobutene from *Maprounea Africana*. *Tetrahedron Lett.* **1993**, *34*, 4461−4464. (c) Fokialakis, N.; Magiatis, P.; Terzis, A.; Tillequin, F.; Skaltsounis, A.-L. Cyclomegistine, the First Alkaloid with the New Cyclobuta[*b*]-quinoline ring System from Sarcomelicope Megistophylla. *Tetrahedron Lett.* **2001**, *42*, 5323−5325.

(2) For the review, see: (a) Chen, J.; Zhou, Q.; Fang, H.; Lu, P. Dancing on Ropes − Enantioselective Functionalization of Preformed Four-Membered Carbocycles. *Chin. J. Chem.* **2022**, *40*, 1346−1358. For selected examples, see: (b) Eisold, M.; Didier, D. Highly Diastereoselective Synthesis of Methylenecyclobutanes by Merging Boron-Homologation and Boron-Allylation Strategies. *Angew. Chem., Int. Ed.* **2015**, *54*, 15884−15887. (c) Nóvoa, L.; Trulli, L.; Parra, A.; Tortosa, M. Stereoselective Diboration of Spirocyclobutenes: A Platform for the Synthesis of Spirocycles with Orthogonal Exit Vectors. *Angew. Chem., Int. Ed.* **2021**, *60*, 11763−11768. (d) Liang, Z.; Wang, L.; Wang, Y.; Wang, L.; Chong, Q.; Meng, F. Cobalt-Catalyzed Diastereo- and Enantioselective Carbon-Carbon Bond Forming Reactions of Cyclobutenes. *J. Am. Chem. Soc.* **2023**, *145*, 3588−3598.

(3) For selected reviews, see: (a) Xu, Y.; Conner, M. L.; Brown, M. K. Cyclobutane and Cyclobutene Synthesis: Catalytic Enantioselective [2 + 2] Cycloadditions. *Angew. Chem., Int. Ed.* **2015**, *54*, 11918−11928. (b) Misale, A.; Niyomchon, S.; Maulide, N. Cyclobutenes: At a Crossroad between Diastereoselective Syntheses of Dienes and Unique Palladium-Catalyzed Asymmetric Allylic Substitutions. *Acc. Chem. Res.* **2016**, *49*, 2444−2458. (c) Didier, D.; Reiners, F. Uncommon Four-Membered Building Blocks - Cyclobutenes, Azetines and Thietes. *Chem. Rec.* **2021**, *21*, 1144−1160. For selected examples, see: (d) Narasaka, K.; Hayashi, Y.; Shimadzu, H.; Niihata, S. Asymmetric [2 + 2] Cycloaddition Reaction Catalyzed by a Chiral Titanium Reagent. *J. Am. Chem. Soc.* **1992**, *114*, 8869−8885. (e) Fan, B.-M.; Li, X.-J.; Peng, F.-Z.; Zhang, H.-B.; Chan, A. S. C.; Shao, Z.-H. Ligand-Controlled Enantioselective [2 + 2] Cycloaddition of Oxabicyclic Alkenes with Terminal Alkynes Using Chiral Iridium Catalysts. *Org. Lett.* **2010**, *12*, 304−306. (f) García-Morales, C.; Ranieri, B.; Escofet, I.; López-Suarez, L.; Obradors, C.; Konovalov, A. I.; Echavarren, A. M. Enantioselective Synthesis of Cyclobutenes by Intermolecular [2 + 2] Cycloaddition with Non-C_2 Symmetric Digold Catalysts. *J. Am. Chem. Soc.* **2017**, *139*, 13628−13631. (g) Kossler, D.; Perrin, F. G.; Suleymanov, A. A.; Kiefer, G.; Scopelliti, R.; Severin, K.; Cramer, N. Divergent Asymmetric Synthesis of Polycyclic Compounds via Vinyl Triazenes. *Angew. Chem., Int. Ed.* **2017**, *56*, 11490−11493. (h) Jiao, Z.; Shi, Q.; Zhou, J. S. Asymmetric Intermolecular Heck Reaction of Propargylic Acetates and Cycloalkenes to Access Fused Cyclobutenes. *Angew. Chem., Int. Ed.* **2017**, *56*, 14567−14571. (i) Kossler, D.; Cramer, N. Neutral Chiral Cyclopentadienyl Ru(II)Cl Catalysts Enable Enantioselective [2 + 2]-Cycloadditions. *Chem. Sci.* **2017**, *8*, 1862−1866. (j) Cañellas, S.; Montgomery, J.; Pericàs, M. À. Nickel-Catalyzed Reductive [2 + 2] Cycloaddition of Alkynes. *J. Am. Chem. Soc.* **2018**, *140*, 17349−17355. (k) Parsutkar, M. M.; Pagar, V. V.; RajanBabu, T. V. Catalytic Enantioselective Synthesis of Cyclobutenes from Alkynes and Alkenyl Derivatives. *J. Am. Chem. Soc.* **2019**, *141*, 15367−15377. (l) Luparia, M.; Oliveira, M. T.; Audisio, D.; Frébault, F.; Goddard, R.; Maulide, N. Catalytic Asymmetric Diastereodivergent Deracemization. *Angew. Chem., Int. Ed.* **2011**, *50*, 12631−12635. (m) Yuan, Y.-G.; Ren, S.-K.; Qiu, Z.-Z.; Wang, S.-W.; Xie, Z.-W. Synthesis of Carborane-Fused Cyclobutenes and Cyclobutanes. *Sci. China Chem.* **2014**, *57*, 1157−1163. (n) Zhang, F.-G.; Marek, I. Brook Rearrangement as Trigger for Carbene Generation: Synthesis of Stereodefined and Fully Substituted Cyclobutenes. *J. Am. Chem. Soc.* **2017**, *139*, 8364−8370. (o) Deng, Y.; Massey, L. A.; Zavalij, P. Y.; Doyle, M. P. Catalytic Asymmetric [3 + 1]-Cycloaddition Reaction of Ylides with Electrophilic Metalloenolcarbene Intermediates. *Angew. Chem., Int. Ed.* **2017**, *56*, 7479−7483. (p) Wen, K.-G.; Liu, C.; Wei, D.-H.; Niu, Y.-F.; Peng, Y.-Y.; Zeng, X.-P. Catalytic Enantioselective Desymmetrization of Cyclobutane-1,3-diones by Carbonyl-Amine Condensation. *Org. Lett.* **2021**, *23*, 1118−1122.

(4) Maturi, M. M.; Bach, T. Enantioselective Catalysis of the Intermolecular [2 + 2] Photocycloaddition between 2-Pyridones and Acetylenedicarboxylates. *Angew. Chem., Int. Ed.* **2014**, *53*, 7661−7664.

(5) (a) List, B.; Lerner, R. A.; Barbas, C. F. Proline-Catalyzed Direct Asymmetric Aldol Reactions. *J. Am. Chem. Soc.* **2000**, *122*, 2395−2396. (b) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. New Strategies for Organic Catalysis: The First Highly Enantioselective Organocatalytic Diels-Alder Reaction. *J. Am. Chem. Soc.* **2000**, *122*, 4243−4244. (c) List, B. Introduction: Organocatalysis. *Chem. Rev.* **2007**, *107*, 5413−5415. (d) MacMillan, D. W. C. The Advent and Development of Organocatalysis. *Nature* **2008**, *455*, 304−308. (e) Xiao, X.; Xu, K.; Gao, Z.-H.; Zhu, Z.-H.; Ye, C.; Zhao, B.; Luo, S.; Ye, S.; Zhou, Y.-G.; Xu, S.; Zhu, S.-F.; Bao, H.-L.; Sun, W.; Wang, X.; Ding, K. Biomimetic Asymmetric Catalysis. *Sci. China Chem.* **2023**, *66*, 1553−1633.

(6) (a) Lorton, C.; Castanheiro, T.; Voituriez, A. Catalytic and Asymmetric Process via P^{III}/P^{V}=O Redox Cycling: Access to (Trifluoromethyl)cyclobutenes via a Michael Addition/Wittig Olefination Reaction. *J. Am. Chem. Soc.* **2019**, *141*, 10142−10147. (b) Lorton, C.; Roblin, A.; Retailleau, P.; Voituriez, A. Synthesis of Functionalized Cyclobutenes and Spirocycles via Asymmetric P(III)/P(V) Redox Catalysis. *Adv. Syn. Catal.* **2021**, *363*, 4805−4810. (c) Zhang, M.; Wang, X.-C. Bifunctional Borane Catalysis of a Hydride Transfer/Enantioselective [2 + 2] Cycloaddition Cascade. *Angew. Chem., Int. Ed.* **2021**, *60*, 17185−17190.

(7) Walczak, M. A. A.; Krainz, T.; Wipf, P. Ring-Strain-Enabled Reaction Discovery: New Heterocycles from Bicyclo[1.1.0]butanes. *Acc. Chem. Res.* **2015**, *48*, 1149−1158.
(8) (a) Kelly, C. B.; Milligan, J. A.; Tilley, L. J.; Sodano, T. M. Bicyclobutanes: from Curiosities to Versatile Reagents and Covalent Warheads. *Chem. Sci.* **2022**, *13*, 11721−11737. (b) Golfmann, M.; Walker, J. C. L. Bicyclobutanes as Unusual Building Blocks for Complexity Generation in Organic Synthesis. *Commun. Chem.* **2023**, *6*, 9.
(9) For selected recent examples, see: (a) McNamee, R. E.; Thompson, A. L.; Anderson, E. A. Synthesis and Applications of Polysubstituted Bicyclo[1.1.0]butanes. *J. Am. Chem. Soc.* **2021**, *143*, 21246−21251. (b) Kerner, M. J.; Wipf, P. Semipinacol-Type Rearrangements of [3-(Arylsulfonyl)bicyclo[1.1.0]butan-1-yl]-alkanols. *Org. Lett.* **2021**, *23*, 3615−3619. (c) Kleinmans, R.; Pinkert, T.; Dutta, S.; Paulisch, T. O.; Keum, H.; Daniliuc, C. G.; Glorius, F. Intermolecular [2π+2σ]-Photocycloaddition Enabled by Triplet Energy Transfer. *Nature* **2022**, *605*, 477−482. (d) Bychek, R.; Mykhailiuk, P. K. A Practical and Scalable Approach to Fluoro-Substituted Bicyclo[1.1.1]pentanes. *Angew. Chem., Int. Ed.* **2022**, *61*, No. e202205103. (e) Guo, R.; Chang, Y.-C.; Herter, L.; Salome, C.; Braley, S. E.; Fessard, T. C.; Brown, M. K. Strain-Release [2π+2σ] Cycloadditions for the Synthesis of Bicyclo[2.1.1]hexanes Initiated by Energy Transfer. *J. Am. Chem. Soc.* **2022**, *144*, 7988−7994. (f) Liang, Y.; Kleinmans, R.; Daniliuc, C. G.; Glorius, F. Synthesis of Polysubstituted 2-Oxabicyclo[2.1.1]hexanes via Visible-Light-Induced Energy Transfer. *J. Am. Chem. Soc.* **2022**, *144*, 20207−20213. (g) Zheng, Y.; Huang, W.; Dhungana, R. K.; Granados, A.; Keess, S.; Makvandi, M.; Molander, G. A. Photochemical Intermolecular [3σ+2σ]-Cycloaddition for the Construction of Aminobicyclo[3.1.1]-heptanes. *J. Am. Chem. Soc.* **2022**, *144*, 23685−23690. (h) Wang, M.; Huang, Y.; Li, C.; Lu, P. Diastereoselective Synthesis of 1,1,3,3-Tetrasubstituted Cyclobutanes Enabled by Cycloaddition of Bicyclo[1.1.0]butanes. *Org. Chem. Front.* **2022**, *9*, 2149−2153. (i) Chen, P.-P.; Wipf, P.; Houk, K. N. How Mono- and Diphosphine Ligands Alter Regioselectivity of the Rh-Catalyzed Annulative Cleavage of Bicyclo[1.1.0]butanes. *Nat. Commun.* **2022**, *13*, 7292. (j) Agasti, S.; Beltran, F.; Pye, E.; Kaltsoyannis, N.; Crisenza, G. E. M.; Procter, D. J. A Catalytic Alkene Insertion Approach to Bicyclo[2.1.1]hexane Bioisosteres. *Nat. Chem.* **2023**, *15*, 535−541. (k) Yu, T.; Yang, J.; Wang, Z.; Ding, Z.; Xu, M.; Wen, J.; Xu, L.; Li, P. Selective [2σ+2σ] Cycloaddition Enabled by Boronyl Radical Catalysis: Synthesis of Highly Substituted Bicyclo[3.1.1]heptanes. *J. Am. Chem. Soc.* **2023**, *145*, 4304−4310. (l) Wölfl, B.; Winter, N.; Li, J.; Noble, A.; Aggarwal, V. K. Strain-Release Driven Epoxidation and Aziridination of Bicyclo[1.1.0]butanes via Palladium Catalyzed σ-Bond Nucleopalladation. *Angew. Chem., Int. Ed.* **2023**, *62*, No. e202217064. (m) Radhoff, N.; Daniliuc, C. G.; Studer, A. Lewis Acid Catalyzed Formal (3 + 2)-Cycloaddition of Bicyclo[1.1.0]butanes with Ketenes. *Angew. Chem., Int. Ed.* **2023**, *62*, No. e202304771. (n) Liang, Y.; Paulus, F.; Daniliuc, C. G.; Glorius, F. Catalytic Formal [2π+2σ] Cycloaddition of Aldehydes with Bicyclobutanes: Expedient Access to Polysubstituted 2-Oxabicyclo[2.1.1]hexanes. *Angew. Chem., Int. Ed.* **2023**, *62*, No. e202305043.
(10) Becknell, A. F.; Berson, J. A.; Srinivasan, R. Competing Pathways in the Photolysis of Bicyclo[1.1.0]butane. *J. Am. Chem. Soc.* **1985**, *107*, 1076−1078.
(11) Dhake, K.; Woelk, K. J.; Becica, J.; Un, A.; Jenny, S. E.; Leitch, D. C. Beyond Bioisosteres: Divergent Synthesis of Azabicyclohexanes and Cyclobutenyl Amines from Bicyclobutanes. *Angew. Chem., Int. Ed.* **2022**, *61*, No. e202204719.
(12) Maercker, A.; Oeffner, K. S.; Girreser, U. Polylithiumorganic Compounds. Part 29: C,C Bond Cleavage of Phenyl Substituted and Strained Carbocycles Using Lithium Metal. *Tetrahedron* **2004**, *60*, 8245−8256.
(13) Livingstone, K.; Siebold, K.; Meyer, S.; Martín-Heras, V.; Daniliuc, C. G.; Gilmour, R. Skeletal Ring Contractions via I(I)/I(III) Catalysis: Stereoselective Synthesis of *cis*-α,α-Difluorocyclopropanes. *ACS Catal.* **2022**, *12*, 14507−14516.
(14) McNamee, R. E.; Haugland, M. M.; Nugent, J.; Chan, R.; Christensen, K. E.; Anderson, E. A. Synthesis of 1,3-Disubstituted Bicyclo[1.1.0]butanes via Directed Bridgehead Functionalization. *Chem. Sci.* **2021**, *12*, 7480−7485.
(15) (a) Zhong, C.; Huang, Y.; Zhang, H.; Zhou, Q.; Liu, Y.; Lu, P. Enantioselective Synthesis of 3-Substituted Cyclobutenes by Catalytic Conjugate Addition/Trapping Strategies. *Angew. Chem., Int. Ed.* **2020**, *59*, 2750−2754. (b) Ning, X.; Chen, Y.; Hu, F.; Xia, Y. Palladium-Catalyzed Carbene Coupling Reactions of Cyclobutanone *N*-Sulfonylhydrazones. *Org. Lett.* **2021**, *23*, 8348−8352. (c) Yan, X.; Zhu, Y.; Xia, Y. Nickel-Catalyzed Tunable Enantioconvergence and Kinetic Resolution in the Coupling of Tertiary Cyclobutenols with Arylboroxines. *Angew. Chem., Int. Ed.* **2023**, *62*, No. e202304462. (d) Egea-Arrebola, D.; Goetzke, F. W.; Fletcher, S. P. Rhodium-Catalyzed Asymmetric Arylation of Cyclobutenone Ketals. *Angew. Chem., Int. Ed.* **2023**, *62*, No. e202217381.
(16) (a) Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. Enantioselective Mannich-Type Reaction Catalyzed by a Chiral Brønsted Acid. *Angew. Chem., Int. Ed.* **2004**, *43*, 1566−1568. (b) Uraguchi, D.; Terada, M. Chiral Brønsted Acid-Catalyzed Direct Mannich Reactions Via Electrophilic Activation. *J. Am. Chem. Soc.* **2004**, *126*, 5356−5357. (c) Akiyama, T. Stronger Brønsted Acids. *Chem. Rev.* **2007**, *107*, 5744−5758. (d) Parmar, D.; Sugiono, E.; Raja, S.; Rueping, M. Complete Field Guide to Asymmetric BINOL-Phosphate Derived Brønsted Acid and Metal Catalysis: History and Classification by Mode of Activation; Brønsted Acidity, Hydrogen Bonding, Ion Pairing, and Metal Phosphates. *Chem. Rev.* **2014**, *114*, 9047−9153. (e) Cheng, J. K.; Xiang, S.-H.; Tan, B. Imidodiphosphorimidates (IDPis): Catalyst Motifs with Unprecedented Reactivity and Selectivity. *Chin. J. Chem.* **2023**, *41*, 685−694.
(17) (a) Nakashima, D.; Yamamoto, H. Design of Chiral *N*-Triflyl Phosphoramide as a Strong Chiral Brønsted Acid and Its Application to Asymmetric Diels−Alder Reaction. *J. Am. Chem. Soc.* **2006**, *128*, 9626−9627. (b) Caballero-García, G.; Goodman, J. M. *N*-Triflylphosphoramides: Highly Acidic Catalysts for Asymmetric Transformations. *Org. Biomol. Chem.* **2021**, *19*, 9565−9618.
(18) (a) Liu, Y.; Song, R.; Li, J. The cycloaddition reaction using visible light photoredox catalysis. *Sci. China Chem.* **2016**, *59*, 161−170. (b) Muriel, B.; Gagnebin, A.; Waser, J. Synthesis of Bicyclo[3.1.0]hexanes by (3 + 2) Annulation of Cyclopropenes with Aminocyclopropanes. *Chem. Sci.* **2019**, *10*, 10716−10722.
(19) Guin, A.; Bhattacharjee, S.; Harariya, M. S.; Biju, A. T. Lewis Acid-Catalyzed Diastereoselective Carbofunctionalization of Bicyclobutanes Employing Naphthols. *Chem. Sci.* **2023**, *14*, 6585.
(20) (a) Hansch, C.; Leo, A.; Taft, R. W. A Survey of Hammett Substituent Constants and Resonance and Field Parameters. *Chem. Rev.* **1991**, *91*, 165−195. (b) Maji, R.; Ghosh, S.; Grossmann, O.; Zhang, P.; Leutzsch, M.; Tsuji, N.; List, B. A Catalytic Asymmetric Hydrolactonization. *J. Am. Chem. Soc.* **2023**, *145*, 8788−8793.
(21) Li, Y.-P.; Zhu, S.-F.; Zhou, Q.-L. Chiral Spiro Phosphoramide-Catalyzed Sulfa-Michael Addition/Enantioselective Protonation of Exocyclic Enones. *Org. Lett.* **2019**, *21*, 9391−9395.

https://doi.org/10.1021/jacs.3c06525
J. Am. Chem. Soc. 2023, 145, 21152−21158