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Brønsted acid-catalyzed synthesis of spirocyclobutanes *via* heteroannulation of vinyloxyphenylbicyclobutanes with water

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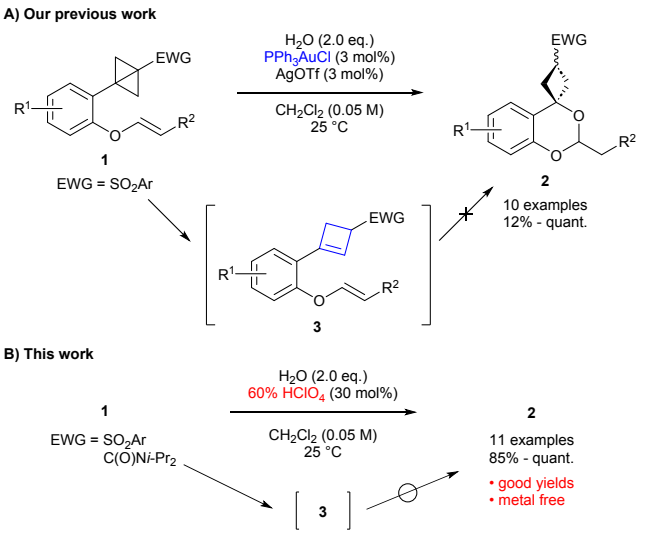
We report a perchloric acid-catalyzed heteroannulation for the synthesis of spirocyclobutanes using vinyloxyphenylbicyclobutanes with water. This metal-free reaction yields high product outputs and is consistent with the formation of a cyclobutene intermediate originating from an isomerization of a bicyclobutane.

Cyclobutane is a square compound consisting of four carbons and has a characteristic three-dimensional structure with restricted steric flexibility. The cyclobutane skeleton is also found in natural products, and its structural features are expected to be utilized in drug discovery.[1] On the other hand, bicyclobutane[2] is a fascinating and unique organic compound with distinctive structural and chemical properties. It belongs to the class of cycloalkanes, specifically a bicyclic compound, as it consists of two fused cyclopropanes. The high ring strain in bicyclobutane makes it a reactive and unstable compound,[3] which can undergo various reactions to relieve the strain and achieve a more stable conformation. The versatile reactivity of bicyclobutanes enables them to serve as flexible building blocks for a variety of structural targets, ranging from relatively straightforward cyclobutanes to intricate bridged, fused, and spirocyclic systems.[4] Derivatization reactions that preserve the highly strained core are also achievable.

To date, we have been advancing research with a focus on developing cyclization reactions using compounds possessing multiple reactive sites within the molecule as substrates.[5] Our interest lies in the synthesis of functionalized, complex cyclic compounds, with the goal of achieving functional molecule synthesis. Regarding the research involving the utilization of bicyclobutane derivatives, we have recently achieved success in the development of cyclization reactions of bicyclobutane derivatives using a gold catalyst, affording spirocyclic compounds composed of cyclic acetals and cyclobutane (Scheme 1A).[5e] However, there was a problem of generally low yields in the substrate scope. The primary issue was that the bicyclobutane derivatives isomerized into cyclobutenes *in situ*, thereby inhibiting the heteroannulation reaction. Additionally, the requirement for expensive transition metal catalysts was also a concern. To achieve a more convenient and metal-free process, we focused on the activation of enol ethers by Brønsted acids.[6]



Scheme 1 Heteroannulation of bicyclobutane derivative **1** with water.

When water is added to activated enol ethers, hemiacetals are formed, and their reverse reaction or decomposition often becomes an issue.[7] Additionally, it is known that bicyclobutanes isomerize to cyclobutenes under Brønsted acid conditions.[8] In this context, we decided to explore the conditions under which the hemiacetals formed in situ could react intramolecularly with

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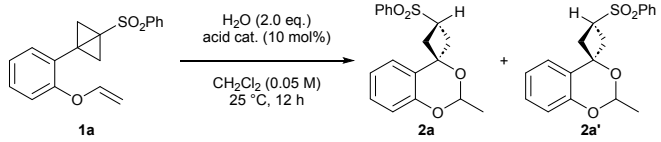
bicyclobutane or cyclobutene. Thereby, we discovered that the heteroannulation reaction of bicyclobutane **1**, catalyzed by the easily manageable perchloric acid, proceeded smoothly (Scheme 1B). The use of perchloric acid not only simplified the reaction conditions but also enhanced the product yields in the substrate scope. Furthermore, we observed differences in the reaction mechanism compared to that of the gold-catalyzed reaction.

We evaluated various Brønsted acids as catalysts for the heteroannulation of **1a** with water in dichloromethane at ambient temperature (Table 1). Utilizing formic acid and diphenyl phosphate led to the formation of compounds **2a** and **2a'** with yields of 24% and 27%, respectively (entries 1 and 2).[9] In contrast, employing trifluoroacetic acid (TFA) and *p*-toluenesulfonic acid (PTSA), both having comparable pKa values, resulted in negligible product formation with TFA (entry 3) and a 76% yield of the desired product with PTSA (entry 4). Exploring aqueous solutions of four distinct strong acids (entries 5-8) revealed that perchloric acid ($HClO_4$) was most effective, producing the cyclized compound in 94% yield with a 0.94:1 ratio of **2a** to **2a'** (entry 7). Utilization of more potent acids, such as sulfuric acid (H_2SO_4) and trifluoromethanesulfonic acid (CF_3SO_3H), did not enhance the yield (entries 8 and 9). Subsequently, a higher catalyst loading of $HClO_4$ (30 mol%) further increased the yield to 98% yield with a 1.01:1 ratio of **2a**/**2a'** (entry 10).

Table 1 Screening of acid catalysts[a]

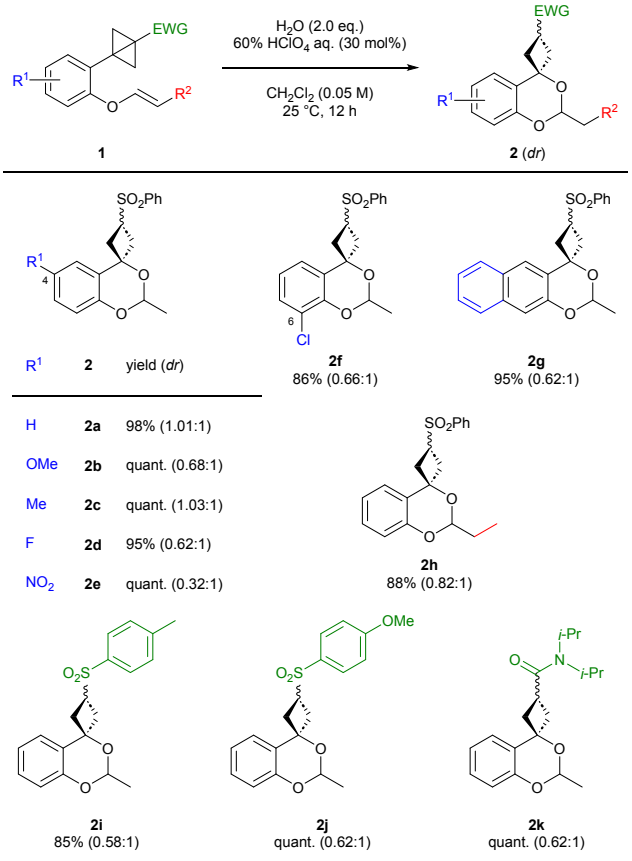


1a 2a 2a'

Entry	Acid cat.	Yield (%, **2a**:**2a'**)[b]
1	HCOOH	24 (0.30:1)
2	$(PhO)_2P(O)OH$	27 (0.12:1)
3	CF_3COOH	trace
4	*p*-$MeC_6H_4SO_3H \cdot H_2O$	76 (0.61:1)
5	60% HNO_3 aq.	73 (0.86:1)
6	conc. HCl	trace
7	60% $HClO_4$ aq.	94 (0.94:1)
8	conc. H_2SO_4	10 (0.16:1)
9	CF_3SO_3H	70 (0.31:1)
10[c]	60% $HClO_4$ aq.	98[d] (1.01:1)

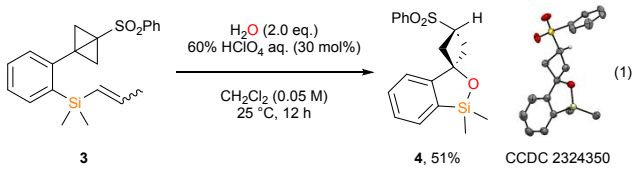
[a]Reaction Conditions: **1a** (0.10 mmol), H_2O (2.0 equiv.), Acid cat. (10 mol.%), CH_2Cl_2 (2.0 mL), 25 °C, 12 h. [b]Yields and diastereomeric ratios were determined *via* ^1H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard. [c]30 mol% of 60% $HClO_4$ aq. was used. [d]Isolated yield (%).

With the optimized reaction conditions, we examined substitution on the aromatic ring for exploring the substrate scope (Table 2).[10] When substrates with electron-donating groups, such as methoxy or methyl, were positioned at the 4-position of the aromatic ring, the cyclization products **2b** and **2c** were obtained quantitatively. In cases where electron-withdrawing groups like fluoro or nitro were used at the 4-position, the cyclization products were produced in high to quantitative yields, with slight variations in diastereoselectivity observed for each substituent (**2d**, **2e**). A substrate with a chloro group at the 6-position resulted in an 86% yield of **2f**. The reaction of naphthalene derivative proceeded smoothly to afford **2g** with a 95% yield. we also examined the scope by varying the substituents on the vinyl ether and the electron-withdrawing group on bicyclobutane. The propenyl ether-type substrate led to the formation of the corresponding cyclization product **2h** with an 88% yield. Modifying the electron-withdrawing group from a phenylsulfonyl group to a *p*-tosyl group (**2i**), a *p*-methoxyphenylsulfonyl group (**2j**), or replacing it with a diisopropylamide group (**2k**), resulted in the formation of the corresponding products in good yields (85%-quant.). The reaction conditions using perchloric acid as the catalyst, compared to the previous gold-catalyzed reactions, were able to afford the products in good to quantitative yields.[11]

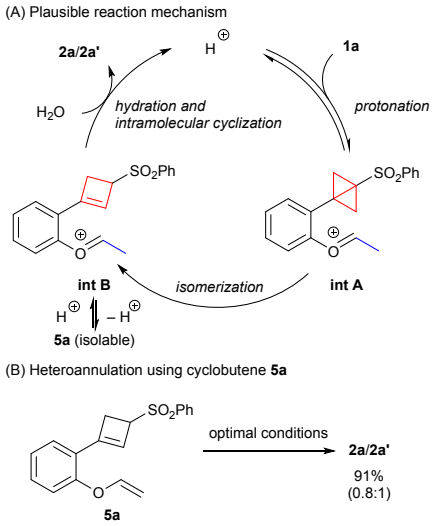


Scheme 2 Substrate scope.

In addition, we conducted a heteroannulation reaction with substrate **3**, in which the vinyl ether moiety was replaced with a dimethylpropenylsilyl group (eq. 1). This modification led to the formation of spirocyclic oxasilole compound **4** with a yield of 51% as a single diastereomer. Its structural characteristics were conclusively determined using X-ray crystallography.



To gain insights into the reaction mechanism of the annulation reaction, we performed NMR experiments to observe the reaction intermediates in deuterated dichloroethane (CD_2Cl_2) (Fig. 1). As a result, in the initial stages of the reaction, shifted singlet peaks of bicyclobutane and peaks of ethylidene oxonium formed by the protonation of the enol ether appeared (~ 2 h), indicating the formation of **int A** (Scheme 3A). At this stage of protonation of the enol ether, the desired product was not observed based on the ^{1}H NMR spectra. Subsequently, **int B** in which bicyclobutane isomerized into cyclobutene was detected, as evidenced by the observation of cyclobutene's alkene protons at approximately 6.2 ppm. Thereafter the product **2a**/**2a'** gradually began to form through the hydration and intramolecular cyclization.[12] It is noteworthy that in this reaction, no decomposition of the hemiacetal intermediates was observed, and the desired product was obtained with good yields due to the rapid intramolecular cyclization reaction. In the course of the reaction, we also observed cyclobutene compound **5a**, which was isolable. When the heteroannulation reaction was carried out using **5a**, the corresponding product **2a**/**2a'** was generated with a comparable yield (Scheme 3B). Therefore, unlike the previous gold-catalyzed reactions, it became clear that under acid-catalyzed conditions, the reaction can proceed *via* the intermediacy of cyclobutene.



Scheme 3 Plausible reaction mechanism.

To discuss the diastereoselectivity of the products, some control experiments were conducted. When the product **2a** or **2a'** was subjected to the heteroannulation reaction conditions, no epimerization and no decomposition were observed (eq. S2 and eq. S3 in SI). Additionally, density functional theory (DFT) calculations were conducted to determine the energies of **2a** and **2a'**, as well as **2e** and **2e'**. In each case, it was found that the isomers of **2** are ca. 4 kcal/mol more stable (details in SI).

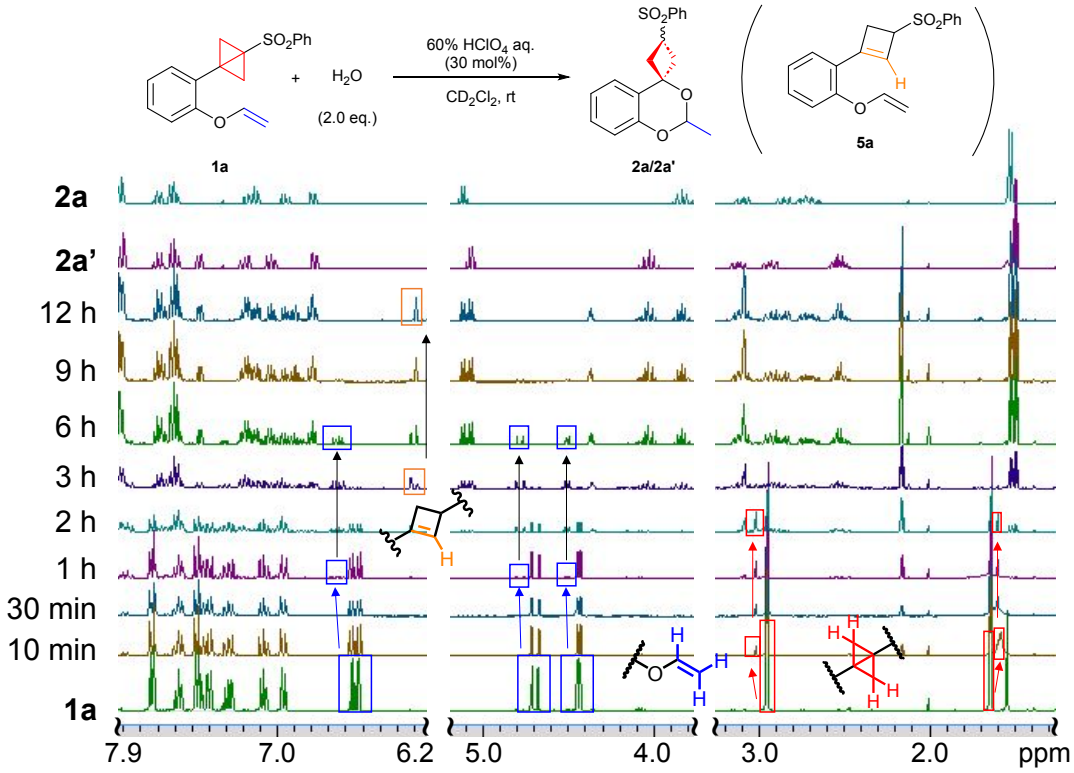


Fig. 1 Time-course NMR studies (conversion from **1a** to **2a**/**2a'**)

Therefore, the diastereoselectivity of the product is presumed to be determined at the cyclization stage.

In conclusion, we found that the heteroannulation of bicyclobutane derivatives **1** with water, in the presence of perchloric acid, efficiently produces spirocyclobutanes **2** under mild conditions. This method is applicable for synthesizing oxasilole compound **4** using silicon-substituted starting materials. Compared to our previous reports, this study provided a methodology that results in high product yields. Additionally, distinct differences in reaction mechanisms were noted, with NMR experiments indicating that heteroannulation can proceed through a cyclobutene intermediate, isomerized from bicyclobutane.

Conceptualization, T. M., M. S.; investigation, methodology and data acquisition and curation, T. M., H. A.; writing –original draft preparation, M. S.; writing – review and editing, T. M., M. A., M. S.; funding acquisition, M. A., M. S.

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Conflicts of interest

There are no conflicts to declare.

Notes and references

1 (a) V. M. Dembitsky, *J. Nat. Med.*, 2008, **62**, 1; (*b*) V. M. Dembitsky, *Phytomedicine*, 2014, **21**, 1559; (*c*) Y. Y. Fan, X. H. Gao and J. M. Yue, *Sci. China: Chem.*, 2016, **59**, 1126; (*d*) L. A. Marchetti, L. K. Kumawat, N. Mao, J. C. Stephens and R. B. P. Elmes, *Chemistry*, 2019, **5**, 1398; (*e*) M. R. Bauer, P. D. Fruscia, S. C. C. Lucas, L. N. Michaelides, J. E. Nelson, R. L. Storer and B. C. Whitehurst, *RSC Med. Chem.*, 2021, **12**, 448; (f) M. R. van der Kolk, M. A. C. H. Janssen, F. P. J. T. Rutjes and D. Blanco-Ania, *ChemMedChem*, 2022, **17**, e202200020; (g) P. Yang, Q. Jia, S. Song and X. Huang, *Nat. Prod. Rep.*, 2023, **40**, 1094.

2 (a) D. M. Lemal, F. Menger and G. W. Clark, *J. Am. Chem. Soc.,* 1963, **85**, 2529; (b) E. P. Blanchard, Jr. and A. Cairncross, *J. Am. Chem. Soc.,* 1966, **88**, 487; (c) H. Mizoguchi and A. Sakakura, *Chem. Lett.,* 2021, **50**, 792; (d) C. B. Kelly, J. A. Milligan, L. J. Tilley and T. M. Sodano, *Chem. Sci.,* 2022, **13**, 11721.

3 (a) E. Vogel, *Angew. Chem. Int. Ed.,* 1963, **2**, 1; (b) K. Mukai, K. Jskizu and B. Gert Kobrichl, *Angew. Chem. Int. Ed.,* 1973, **12**, 464; (c) P. R. Khoury, J. D. Goddard and W. Tam, *Tetrahedron*, 2004, **60**, 8103.

4 Recent reviews: (a) M. A. A. Walczak, T. Krainz and P. Wipf, *Acc. Chem. Res.,* 2015, **48**, 1149; (b) J. M. Anderson, N. D. Measom, J. A. Murphy and D. L. Poole, *Angew. Chem. Int. Ed.*, 2021, **60**, 24754; (c) M. Golfmann and J. C. L. Walker, *Commun. Chem.,* 2023, *6*, 9. Selected primary publications: (d) S. Hoz and D. Aurbach, *Tetrahedron*, 1979, **35**, 881; (e) M. Ueda, M. A. A. Walczak and P. Wipf, *Tetrahedron Lett*., 2008, **49**, 5986; (f) M. A. A. Walczak and P. Wipf, *J. Am. Chem. Soc.,* 2008, **130**, 6924; (g) T. Pinkert, M. Das, M. L. Schrader and F. Glorius, *J. Am. Chem. Soc.*, 2021, **143**, 7648; (h) P.-P. Chen, P. Wipf and K. N. Houk, *Nat. Commun.,* 2022, **13,** 7292; (i) M. Jung, J. E. Muir and V. N. G. Lindsay, *Tetrahedron*, 2023, **134**, 133296; (j) H. Wang, H. Shao, A. Das, S. Dutta, H. T. Chan, C. Daniliuc, K. N. Houk and F. Glorius, *Science*, 2023, **381**, 75; (k) L. Tang, Q.-N. Huang, F. Wu, Y. Xiao, J.-L. Zhou, T.-T. Xu, W.-B. Wu, S. Qu and J.-J. Feng, *Chem. Sci.*, 2023, **14**, 9696; (l) Y. Xiao, T.-T. Xu, J.-L. Zhou, F. Wu, L. Tang, R.-Y. Liu, W.-B. Wu and J.-J. Feng, *Chem. Sci.*, 2023, **14**, 13060.

5 (a) S. Ohno and M. Arisawa, *J. Org. Chem.*, 2020, **85**, 6831; (b) J. Qiu, M. Sako, T. Tanaka, T. Matsuzaki, T. Takehara, T. Suzuki, S. Ohno, K. Murai and M. Arisawa, *Org. Lett.,* 2021, **23**, 4284; (c) Y. Sato, T. Matsuzaki, T. Takehara, M. Sako, T. Suzuki and M. Arisawa, *Chem. Comm.*, 2022, **58**, 415; (d) S. Yoshioka., T. Takehara, T. Suzuki and M. Arisawa, *Chem. - A Eur. J.*, 2023, **29**, e202203556; (e) M. Takatsuki, H. Aoyama, K. Murai, M. Arisawa and M. Sako, *Chem. Commun.*, 2023, **59**, 7467.

6 (a) B. M. Trost and I. Fleming, eds. (1991) *Comprehensive organic synthesis: selectivity, strategy, and efficiency in modern organic chemistry.* Vol. 8. Elsevier; (b) A. R. Katritzky, O. Meth-Cohn and C. W. Rees, eds. (1995) *Comprehensive Organic Functional Group Transformations.* Elsevier.

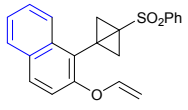
7 (a) I. Smajlagic, B. Carlson and T. Dudding, *J. Org. Chem.*, 2021, **86**, 4171. (b) J. Shin, P. Shum, J. Grey, S. Fujiwara, G. S. Malhotra, A. González-Bonet, S. Hyun, E. Moase, T. M. Allen and D. H. Thompson *Mol. Pharmaceutics*, 2012, **9**, 3266.

8 (a) R. E. McNamee, M. M. Haugland, J. Nugent, R. Chan, K. E. Christensen and E. A. Anderson, *Chem. Sci.*, 2021, **12**, 7480; (b) K. Livingstone, K. Siebold, S. Meyer, V. Martín-Heras, C. G. Daniliuc and R. Gilmour, *ACS Catal.*, 2022, **12**, 14507.

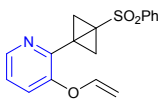
9 The stereostructure of the product was determined by comparison with the previous literature.[5e]

10 Starting materials with electron-donating groups or those without substituents on BCB unit have not been synthesized, and their reactivity has not been investigated.

11 Naphthalene derivative **1l** with a 1,2-substitution pattern and pyridine derivative **1m** did not give the desired products, similar to previous outcomes.



1l



1m

12 Several possible pathways from **Int B** to **2a**/**2a'** were discussed in Scheme S1 (see SI).