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Organo-catalyzed photoelectrochemical ring-contraction of arylidene cyclobutanols via radical cation-triggered semipinacol rearrangement

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The semipinacol rearrangement has proven to be an efficient strategy for converting allylic alcohols into carbonyl compounds bearing an α -quaternary carbon center. Traditionally, this semipinacol rearrangement is initiated through two primary modes, namely electrophile and radical-triggered pathways. Notably, these two strategies predominantly lead to ring-expansion β -functionalized products from cyclic allylic alcohols. In contrast, the radical cation, possessing carbon-centered radical and electrophilic carbocation dual reactivity, potentially triggers ring contraction semipinacol rearrangement of cyclic allylic alcohols, but remains underexplored. This is presumably due to the favorable C–C bond cleavage facilitated by ring-strain release and the challenge associated with overcoming the energy barriers required for ring-contraction. Herein, we report the first photoelectrochemical alkene radical cation-triggered semipinacol rearrangement for the ring-contraction of arylidene cyclobutanols. This methodology enables access to diverse and valuable 1,1-cyclopropane formylketones and diketones under mild and environmentally benign conditions. The resulting products not only contain the cyclopropane motif, which is present in many pharmaceuticals and bioactive molecules, but also serve as useful synthetic intermediates for the preparation of various derivatives, including the key intermediate of cabozantinib.

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Introduction

Rearrangement reactions represent powerful tools for skeletal remodeling. These reactions fundamentally alter the framework by cleaving existing bonds and reorganizing atoms or groups within the molecule. Crucially, rearrangement reactions enable the efficient construction of complex and often difficult-to-access carbon skeletons directly from simple precursors, bypassing multi-step synthetic routes. This capability is particularly valuable in the synthesis of intricate natural products and pharmaceuticals.^{1–4} Among various rearrangement reactions, the semipinacol rearrangement has proven to be an efficient strategy for the transformation of allylic alcohols to carbonyl compounds with an α -quaternary carbon center.^{5–7} Traditionally, the electrophilic attack toward the C=C bond of allylic alcohol generates an electrophilic carbocation, which triggers the subsequent rearrangement, delivering the corresponding carbonyl compounds (Fig. 1A).^{8–18} An alternative strategy involves the radical addition of the C=C bond to form a carbon-centered radical, which is further oxidized to a carbocation

intermediate (radical-polar crossover process), thereby triggering semipinacol rearrangement. This strategy has recently emerged as an efficient platform for the reaction of various radical precursors with allylic alcohols to access diverse β -functionalized ketones *via* photocatalysis^{19–23} or electrocatalysis,^{24–27} among others.^{28–31} Furthermore, both electrophilic and radical functionalization/semipinacol rearrangement sequences typically yield ring-expansion β -functionalized products from cyclic allylic alcohols. This is because the β -C–C bond cleavage of cyclic allylic alcohols is more favored than other transformations due to the release of ring strain. For example, the electrophilic fluorination of arylidene cyclobutanols generated a carbocation intermediate, which tended to undergo C–C bond cleavage, thereby delivering the ring-opening products disclosed by Zhao's group in 2017 (Fig. 1B).³² More recently, the Ackermann,³³ Zhang,³⁴ and our groups³⁵ independently reported that the photocatalytic radical addition of arylidene cyclobutanols led to the same C–C bond cleavage driven by strain release, resulting in the ring-opening products. On the other hand, given the strain energies of 26.3 kcal mol^{–1} for cyclobutanes *versus* 29.0 kcal mol^{–1} for cyclopropanes,³⁶ the ring-contraction of cyclobutanols to access cyclopropanes should be thermodynamically challenging. In 2019, Frongia *et al.* reported the synthesis of cyclopropanecarbaldehydes through a tandem Wittig reaction and

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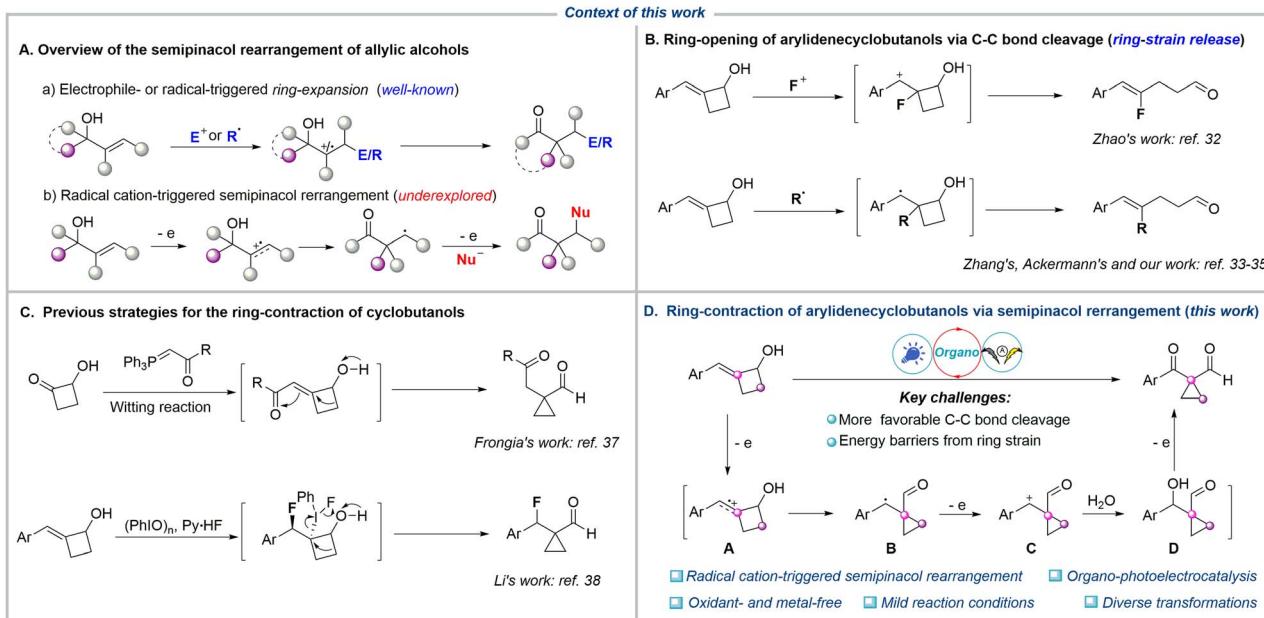


Fig. 1 Context of this work. (A) Overview of the semipinacol rearrangement of allylic alcohols. (B) Ring-opening of arylidenecyclobutanols via C–C bond cleavage. (C) Previous strategies for the ring-contraction of cyclobutanols. (D) Ring-contraction of arylidenecyclobutanols via semipinacol rearrangement (*this work*).

ring-contraction process at 80 °C over 2 days (Fig. 1C).³⁷ Separately, Li and coworkers accomplished a fluorination/semipinacol rearrangement cascade for the ring-contraction of 2-alkylidenecyclobutanol, using a combination of nucleophilic Py·HF and (PhIO)_n.³⁸ Furthermore, alkoxy radical mediated β-C–C bond cleavage of cyclobutanols generates carbon-centered radicals capable of participating in diverse transformations.^{39–47} This competing reaction pathway thereby jeopardizes the desired ring-contraction process. To the best of our knowledge, the radical cation, which features carbon-centered radical and electrophilic carbocation dual reactivity and directly triggers the ring-contraction semipinacol rearrangement of cyclic allylic alcohols, remains underexplored.

Photoelectrochemistry leverages the synergistic integration of light and electrical energy to achieve challenging reactivity and selectivity under mild and environmentally benign conditions.^{48–55} This approach significantly broadens the accessible redox window for reaction design while eliminating dependence on chemical redox reagents, establishing a new paradigm for green and precision organic synthesis. Based on recent achievements in alkene radical cation chemistry^{56–62} and combined with our continuous interest in electrochemical synthesis of cyclopropanes,⁶³ we envisioned that chemoselective oxidation of the C=C bonds in arylidenecyclobutanols could generate the corresponding alkene radical cation **A**, which possesses carbon-centered radical and electrophilic carbocation dual reactivity, and thereby might trigger the semipinacol rearrangement to give the ring-contraction intermediate **B** under suitable conditions (Fig. 1D). Subsequent oxidation of intermediate **B** followed by nucleophilic addition results in the final cyclopropanes, which are important motifs present in

many pharmaceuticals and bioactive molecules.^{64–70} Herein, we report an organo-catalyzed photoelectrochemical ring-contraction of cyclobutanols *via* alkene radical cation triggered-semipinacol rearrangement to access diverse and valuable 1,1-cyclopropane formylketones and diketones with an α-quaternary carbon center under environmentally friendly and mild reaction conditions without the requirement of an oxidant and metal-catalyst.

Results and discussion

The feasibility of our proposal was investigated by employing 2-benzylidenecyclobutanol **1a** as the model substrate under photoelectrochemical conditions (Table 1). After systematically optimizing different reaction parameters, the desired ring-contraction product 1-benzoyl-1-formylcyclopropane **2a** was finally obtained in 72% isolated yield under the following optimal conditions: the photoelectrolysis of **1a** was performed in the presence of 5 mol% 9-mesityl-10-methyl acridinium perchlorate ($[\text{Mes-Acr}^+]\text{ClO}_4^-$) as the catalyst, $^7\text{Bu}_4\text{NPF}_6$ as an electrolyte, Pt plates as the electrode materials in a 5:1:2 $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ mixed solvent at a constant current of 5 mA and 40 W blue light irradiation for 6 hours (Table 1, entry 1). The solvent effect had a decisive influence, as no desired product was detected when using other solvents such as dimethylformamide (DMF) or tetrahydrofuran (THF) instead of CH_3CN (Table 1, entry 2, for more details see SI, Table S1). The electrode materials had a great impact on the reaction efficiency. Switching the cathode material from Pt(–) to Sn(–) or C(–) afforded a decreased yield, whereas on using GF(+) or C(+) as the anode, only a trace amount of the product was observed



Table 1 Optimization of the reaction conditions

Entry		Variation from standard conditions
1		None
2		THF or DMF instead of CH ₃ CN
3		C(–) or Sn(–) instead of Pt(–)
4		C(+) or GF(+) instead of Pt(+)
5		4CzIPN instead of [Mes-Acr ⁺]ClO ₄ [–]
6		Ir(dF(CF ₃)ppy) ₂ (dtbbpy)PF ₆ instead
7		15 W or 35 W instead of 40 W
8		1.0 mL or 1.5 mL H ₂ O instead
9		Et ₄ NPF ₆ or NH ₄ PF ₆ instead
10		3 mA or 8 mA instead of 5 mA
11		TFA or K ₂ CO ₃ as additives
12		No light
13		No catalyst
14		No electricity
Yield ^a of 2a [%]		
1	59 (72) ^b	
2	n.d. ^c	
3	35, 32	
4	Trace, trace	
5	48	
6	52	
7	41, 54	
8	34, 50	
9	42, 58	
10	54, 37	
11	49, 35	
12	31	
13	34	
14	12	

^a GC yields with 1-nitronaphthalene as the internal standard. ^b Isolated yield. ^c n.d. = No desired product was detected.

(Table 1, entries 3 and 4). Among the tested catalysts, including organic dyes, metal photocatalysts, and modifications of [Mes-Acr⁺]ClO₄[–], no better results were obtained (Table 1, entries 5

and 6, for more details see SI, Table S1). Performing the photoelectrochemical reaction with 15 W and 35 W blue LEDs resulted in a diminished yield in both cases (Table 1, entry 7). Slight variations in decreasing or increasing the amount of H₂O had a deleterious influence on the outcome (Table 1, entry 8). The replacement of ⁿBu₄NPF₆ with other electrolytes such as Et₄NPF₆ or NH₄PF₆ led to reduced yields (Table 1, entry 9, for more details see SI, Table S1). In addition, either decreasing or increasing the constant current provided a lower yield (Table 1, entry 10). Furthermore, the addition of trifluoroacetic acid (TFA) or base (K₂CO₃) led to no improvement in the yield (Table 1, entry 11). Control experiments indicated that without light or a catalyst, the yield dropped to 31% or 34%, respectively (Table 1, entries 12 and 13). In addition, electricity is crucial to the reaction since the yield was significantly decreased to 12% without the constant current (Table 1, entry 14). These results indicated that electricity, light as well as the catalyst together guarantee the reaction efficiency. Furthermore, the observation of α,β -unsaturated cyclobutanone and 1-benzoylcyclopropane-1-carboxylic acid as the main byproducts under optimal conditions accounted for the relatively low yield of 2a (see the SI for more details).

With the optimal conditions in hand, we moved our attention to the substrate scope of this photoelectrochemical ring-contraction reaction, as illustrated in Fig. 2. First, we investigated the modifications of the substituents at the *para*-position of the aryl ring of arylidene cyclobutanols. In general, both

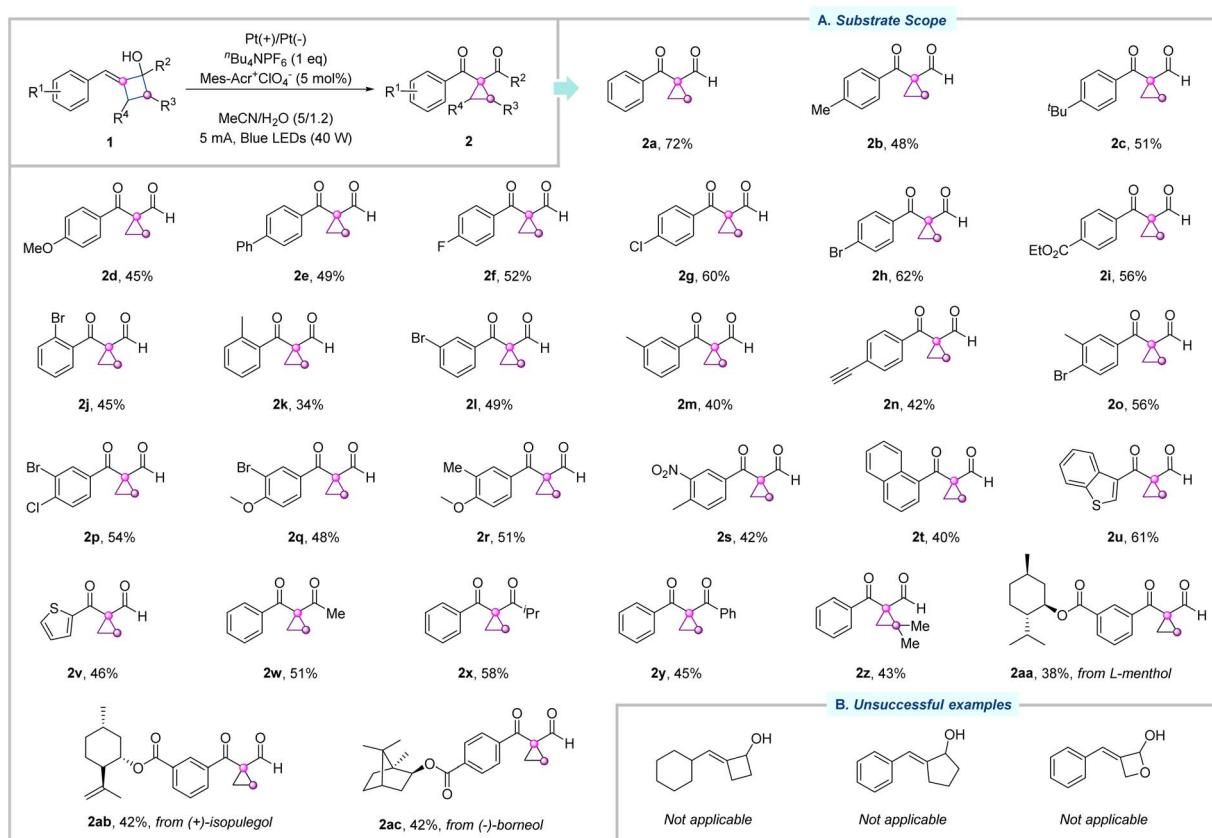


Fig. 2 Substrate scope investigations. (A) Substrate scope. (B) Unsuccessful examples.



electron-donating ($-Me$, $-^tBu$, $-OMe$, and $-Ph$) and electron-withdrawing groups ($-F$, $-Cl$, $-Br$, and $-CO_2Et$) all tolerated very well, delivering the corresponding cyclopropanes **2b–2i** in good yields. Subsequently, the compatibility of functional groups at the *meta* and *ortho* positions of the aryl ring was evaluated. Both electron-donating ($-Me$) and electron-withdrawing ($-Br$) substituents reacted smoothly, affording the desired cyclopropanes **2j–2m** in moderate to good yields. In addition, sensitive functional group alkyne was well tolerated (**2n**). Diverse di-substituted derivatives were applicable to this catalytic reaction, and the desired products (**2o–2s**) were isolated in moderate to good yields. Arylidene cyclobutanols bearing a naphthyl ring, benzothiophene, and thiophene were competent substrates, giving rise to the desired cyclopropanes **2t–2v**. Apart from the above secondary alcohols, tertiary alcohol substrates were subsequently accessed under otherwise identical conditions. Methyl- and isopropyl-substituted arylidene-cyclobutanols **1w** and **1x** were smoothly transformed into **2w** and **2x** in 51% and 58% yields, respectively. Moreover, phenyl-substituted arylidene cyclobutanol **1y** exhibited good reactivity in this photoelectrochemical ring-contraction reaction as well. Arylidene cyclobutanol with a dimethyl group on the four-member ring was suitable under the standard conditions, delivering the cyclopropane derivatives in 43% yield (**2z**). Notably, the photoelectrochemical conditions allowed us to explore substrates derived from more complex molecules, accessing the target cyclopropanes with L-menthol, (+)-isopulegol, and (–)-borneol (**2aa–2ac**). It is noteworthy that the relatively low yields were mainly attributable to the formation of oxidation byproducts that were also observed in the model

reaction. Meanwhile, the reaction suffers from some limitations. The cyclohexyl-substituted cyclobutanol substrate was not well-tolerated, likely due to the instability of the alkyl radical intermediate. Benzylidene cyclopentanol was unsuccessful under the standard conditions. When the substrate containing an oxetane motif was applied to the reaction, the corresponding product was not observed, with the starting materials being completely consumed, indicating that the oxygen atom migration failed under current conditions.

To obtain experimental evidence of the reaction mechanism, we conducted a series of experiments (Fig. 3A). The addition of radical scavengers, including 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) and butylated hydroxytoluene (BHT), both sharply suppressed the formation of the desired product (Fig. 3B). On conducting the reaction with $H_2^{18}O$ instead of H_2O under standard conditions, the heavy-oxygen-labelled product **2a–¹⁸O** was formed, which was confirmed by high-resolution mass spectrometry (HRMS), suggesting that oxygen comes from water and water serves as the nucleophile in the reaction (Fig. 3C). Since substrate **1a** contains a hydroxyl group, which could generate the alkoxy radical under oxidation conditions. This reactive radical can undergo β -scission, radical addition, oxidation, and nucleophilic attack sequences, eventually affording the same product. To rule out this possibility, trimethylsilyl alkenyl cyclobutanol **3** was subjected to the reaction, and product **2a** was isolated in 45% yield, indicating that the alkoxy radical was not involved in the reaction (Fig. 3D). In addition, cyclic voltammetry was employed to identify the oxidation sequence of the alkene and hydroxyl group. Substrate **1a** shows two oxidation peaks at $E = 1.36$ and 2.02 V vs. Ag/AgCl,

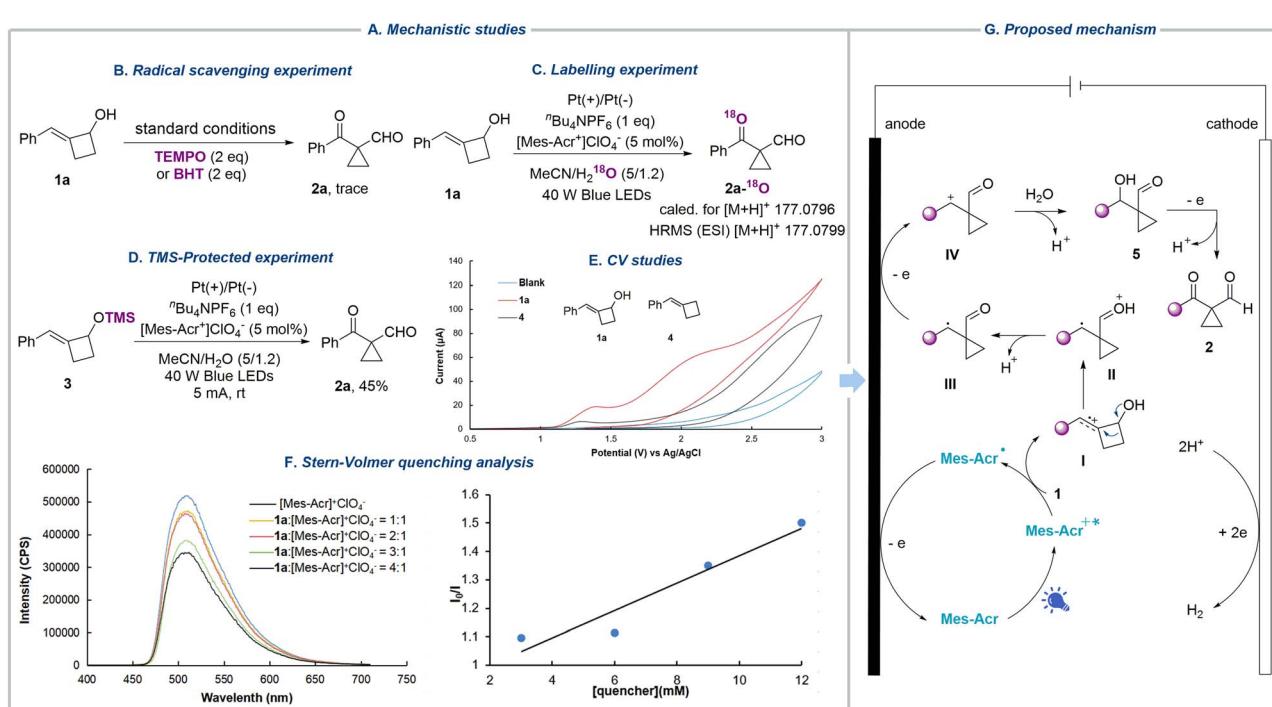


Fig. 3 Mechanistic studies and proposal. (A) Mechanistic studies. (B) Radical scavenging experiment. (C) Labelling experiment. (D) TMS-protected experiment. (E) CV studies. (F) Stern–Volmer quenching analysis. (G) Proposed mechanism.



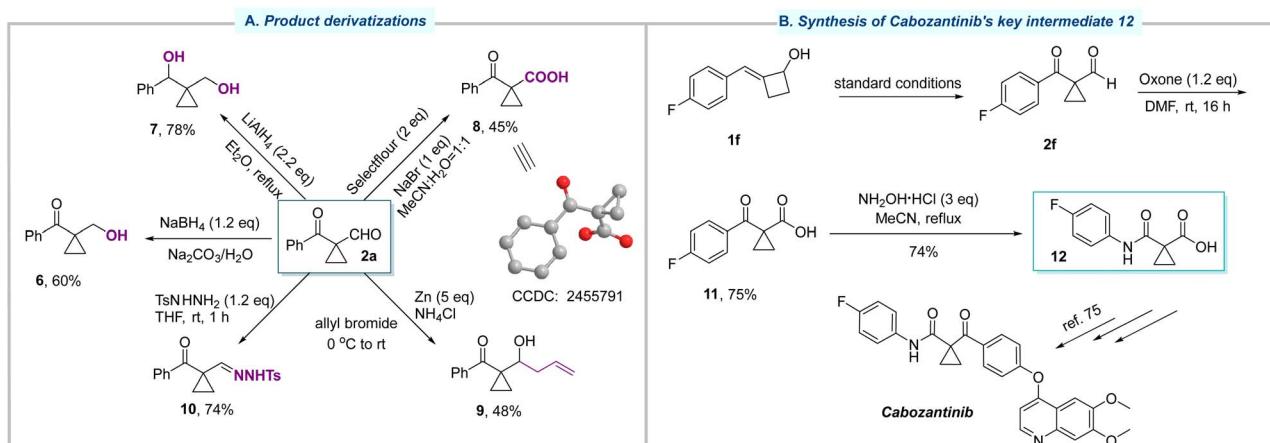


Fig. 4 Synthetic applications. (A) Product derivatizations. (B) Synthesis of cabozantinib's key intermediate 12.

whereas benzylidene cyclobutane **4** presents an oxidation peak at 1.29 V vs. Ag/AgCl, demonstrating the preferential oxidation of the alkene bond of **1** (Fig. 3E). Furthermore, the luminescence quenching experiments were performed with **1a** and $[\text{Mes-Acr}^+]\text{ClO}_4^-$ (Fig. 3F). The results showed that the excited state of $[\text{Mes-Acr}^+]\text{ClO}_4^-$ was quenched by **1a**, signifying that **1a** was oxidized by the excited photocatalyst (see the SI for more details).

Based on the above data and previous work,^{71–73} we propose the mechanism of this photoelectrochemically driven semipinacol-type rearrangement reaction as shown in Fig. 3G. Initially, the excited-state organic dye photocatalyst Mes-Acr^{**} ($E^{\text{red}} = 2.06$ V vs. SCE in MeCN)⁷⁴ could sufficiently oxidize the double bond of **1** to generate the radical cation **I** and the acridinyl radical Mes-Acr[·], which is oxidized at the anode to regenerate the ground-state organocatalyst Mes-Acr⁺. The radical cation **I**, featuring carbon-centered radical and electrophilic carbocation dual reactivity, undergoes semipinacol-type rearrangement to give the oxonium ion intermediate **II**, which then transforms into the carbon-centered radical **III** after the loss of a proton. Subsequently, radical **III** is further oxidized to give the cation intermediate **IV**, which is attacked by H₂O acting as a nucleophile, resulting in the formation of **5** followed by deprotonation. Compound **5** was observed during the reaction, which disappeared after the completion of the reaction (see the SI for more details). Finally, the third anodic oxidation delivers cyclopropanes **2**.

As illustrated in Fig. 4A, further transformations of these 1,1-disubstituted cyclopropanes were investigated to highlight their synthetic utility. First, the formyl group in **2a** could be chemoselectively reduced by NaBH₄ to give **6** in 60% yield. Using a stronger reductant, LiAlH₄, the carbonyl group was also reduced, leading to the formation of diol **7** in 78% yield. On the other hand, the oxidation of **2a** proceeded smoothly and afforded the acid **8**, whose structure was determined by X-ray crystallographic analysis. The reaction of compound **2a** with allyl bromide in the presence of Zn successfully gave rise to allylic alcohol **9**. Moreover, the condensation reaction of **2a** between TsNNH₂ yielded the corresponding tosylhydrazone **10** in 74%

yield. Finally, the oxidation of **2f** with Oxone afforded compound **11** in 75% yield (Fig. 4B). The subsequent Beckmann rearrangement successfully delivered compound **12**, a key intermediate toward the synthesis of cabozantinib.⁷⁵ This alternative synthetic route demonstrated the practicality of this methodology, featuring an advantage that eliminates the use of corrosive and toxic SOCl₂.

Conclusions

In conclusion, we have developed the photoelectrochemical ring-contraction of arylidene cyclobutanols for the first time. This strategy provides a mild and environmentally benign route to a wide range of valuable 1,1-cyclopropane formylketones and diketones bearing an α -quaternary carbon center. Mechanistic investigations indicated that the alkene radical cation-triggered semipinacol rearrangements, deprotonation, oxidation, and nucleophilic attack sequences enable the desired cyclopropanes. The obtained products could serve as versatile synthetic intermediates, as demonstrated by their application in synthesizing a key intermediate of cabozantinib.

Author contributions

Y. Z. and S. H. contributed to the conception and design of the experiments. Y. Z. directed the project and analyzed the data. C. C., X. Z., and G. D. performed the experiments and analyzed the data. Y. Z. wrote the manuscript. Y. L. and S. H. provided valuable suggestions to the project. All authors discussed the results and commented on the manuscript.

Conflicts of interest

There are no conflicts to declare.

Data availability

CCDC 2455791 (8) contains the supplementary crystallographic data for this paper.⁷⁶



The data supporting this article have been included as part of the supplementary information (SI). Supplementary information: experimental procedures and characterization data. See DOI: <https://doi.org/10.1039/d5sc07637d>

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