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Photochemical α-selective radical ring-opening reactions of 1,3-disubstituted acyl bicyclobutanes with alkyl halides: modular access to functionalized cyclobutenes†

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Although ring-opening reactions of bicyclobutanes bearing electron-withdrawing groups, typically with β-selectivity, have evolved as a powerful platform for synthesis of cyclobutanes, their application in the synthesis of cyclobutenes remains underdeveloped. Here, a novel visible light induced α-selective radical ring-opening reaction of 1,3-disubstituted acyl bicyclobutanes with alkyl radical precursors for the synthesis of functionalized cyclobutenes is described. In particular, primary, secondary, and tertiary alkyl halides are all suitable substrates for this photocatalytic transformation, providing ready access to cyclobutenes with a single all-carbon quaternary center, or with two contiguous centers under mild reaction conditions.

Introduction

Four-membered rings such as cyclobutanes and cyclobutenes are important frameworks found in an array of natural products and pharmaceuticals with diverse biological and medicinal properties (Scheme 1a).[1] Meanwhile, they also serve as key intermediates in the synthesis of structurally complex targets.[2] Therefore, the development of new methods for their efficient synthesis has been intensively pursued by the synthetic community. Despite the significant advances made in the area for the synthesis of four-membered rings, modular strategies for the synthesis of these structures remain relatively few in number, particularly in comparison to the available methodologies to synthesize five- and six-membered rings.[3] Specifically, synthesis of multisubstituted functionalized cyclobutanes and cyclobutenes featuring quaternary carbon stereocenters remains challenging.[4]

As the smallest of bicyclic hydrocarbons, bicyclo[1.1.0]butanes (BCBs) are 'spring-loaded' yet bench-stable molecules.[5] The potential energy stored in the bridging bond (66.3 kcal mol^{-1} (calculated))[6] has been harnessed for applications in the design or discovery of new reactions,[7] materials science,[8] medicinal chemistry[9] and analytical chemistry.[10] Among them, BCBs carrying an electron withdrawing group at one end of the bridging bond are often used as substrates in ring-opening reactions with polar carbon[11] and heteroatom-based nucleophiles.[12] In most cases, these reactions occur exclusively at the β-position of the bridging bond, leading to the synthesis of multisubstituted cyclobutanes, as shown in the elegant studies by Gaoni,[11a,12a] Fox,[11b,c] Baran,[12c,d] Wipf,[12e] Aggarwal,[13] Malins,[12f] Biju,[11e] and others (Scheme 1b).[11,12] Besides these, BCBs have been used as a C4 building block for the synthesis of cyclobutanes *via* β-selective ring-opening reactions with radicals.[14] For example, Ernouf and Cintrat presented the application of photoredox-generated nucleophilic secondary (2°) alkyl radicals in reaction with BCBs in 2020. A computational study was performed to compare BCBs with commonly utilized Michael acceptors for the radical addition process, which indicated that the radical addition to the BCB is less favored than the corresponding olefin.[14a] Subsequently, the cyclobutylation reactions of primary (1°) alkyl, tertiary (3°) alkyl and silyl radical precursors with monosubstituted BCBs *via* strain release have been described by Jui,[14b] Lin[14c] & Xia,[14d] and Studer[14e] respectively. Furthermore, the Aggarwal group demonstrated that *in situ* generated BCB boronate complexes can be efficiently attacked by electrophilic trifluoromethyl and α-carbonyl radicals which could be generated by photolysis of C–I bonds.[14f] Of note, a mechanistically distinct homolytic addition reaction of BCBs *via* light-driven cobalt catalysis was demonstrated by Gryko and co-workers.[15] Despite significant progress, the heterolytic- and homolytic strain-release cyclobutylation reaction continues to

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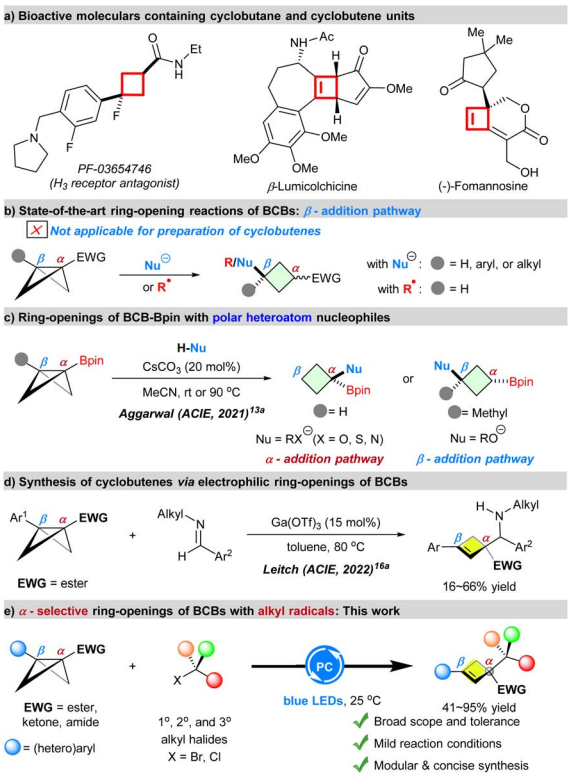

Scheme 1 Ring-opening reactions of BCBs for synthesis of four-membered rings and their scientific context.

face several challenges such as (a) previous reports on the radical ring-openings of BCBs were limited to monosubstituted BCBs. Again, these reactions occur exclusively at the β-position of the bridging bond of BCBs (Scheme 1b);[14] (b) although α-selective ring-opening reactions of monosubstituted bicyclo[1.1.0]butyl boronic ester (BCB-Bpin) with polar heteroatom nucleophiles were reported by Aggarwal and co-workers in 2021, a β-addition pathway was observed when β-methyl-substituted BCB-Bpin was used as the substrate (Scheme 1c).[13a] To the best of our knowledge, there is no report on the α-selective ring-opening reactions of BCBs with radical nucleophiles. (c) So far, most of the transformations have focused on the conjugate addition-type reactivity of BCBs for synthesis of cyclobutanes,[11–14] while less work has been reported on the selective construction of cyclobutenes from BCBs *via* ring-opening reactions.[16] As a rare example, the Leitch group reported Lewis acid catalyzed polar electrophilic ring-opening reactions of BCBs with *N*-alkylimines to generate cyclobutenyl methanamine products with poor to moderate yields (Scheme 1d).[16a] Therefore, discovery of new catalytic systems for efficient synthesis of valuable cyclobutene products is highly desirable.

As part of our ongoing interest in small ring chemistry[17] and in order to expand the library of known BCB reactivity, we became interested in whether 1,3-disubstituted BCBs could be employed as radical acceptors in radical ring-opening reactions. Along this line, other intriguing questions arise: what type of radical substrate is suitable for the reaction? How to control the regioselectivity? Can this reaction lead to cyclobutenes? Here, we describe a modular strategy for the synthesis of functionalized cyclobutenes *via* α-selective ring-opening reactions of acyl BCBs with alkyl radicals, which could be generated from the commercially available 1°, 2°, and 3° alkyl bromides by photolysis of C–Br and C–Cl bonds (Scheme 1e).[18]

Results and discussion

Initial experiments on a representative α-bromo ketone **2a**[18a] and 1,3-disubstituted BCB ester[1a] under the irradiation of blue LEDs revealed that the commonly used metal-based photocatalysts (PCs) ($Ru(bpy)_3Cl_2$, $Ru(bpy)_3(PF_6)_2$, and $Ir[dF(CF_3)ppy]_2[dtbbpy]PF_6$) and organic-based PCs (Eosin Y, $[Acr^+$-Mes$]ClO_4$, and 4-CzIPN) were lowly effective, affording the desired product **3aa** with ≤7% NMR yield (see Table S1, in the ESI†). To our delight, *fac*-$Ir(ppy)_3$ gave a moderate yield of the desired cyclobutene **3aa** along with a 5% yield of **4a** and cyclobutane **5aa** (12% yield) in MeCN (Table 1, entry 1). Importantly, no aimed product **3aa** was observed only with either the *fac*-$Ir(ppy)_3$ catalyst or light, which indicated that photoredox catalysis is essential to this ring-opening process (entries 2 and 6). Subsequent investigations demonstrated the importance of solvent (entries 3–5). The use of DMF as the solvent dramatically improved the yield of **3aa** from 30% to 58% (entry 5 *versus* 1). The base also had a substantial effect on the product distribution but no improvement over K_2HPO_4 was seen (entries 7–10).

Table 1 Optimization of reaction conditions[a]

Entry	Base	Solvent	Yield[b] [%] 3aa	4a	5aa
1	K_3PO_4	MeCN	30	5	12
2[c]	K_3PO_4	MeCN	0	5	0
3	K_3PO_4	THF	43	9	6
4	K_3PO_4	DCE	0	36	<5
5	K_3PO_4	DMF	58	<5	6
6[d]	K_3PO_4	DMF	0	<5	0
7	KH_2PO_4	DMF	30	0	5
8	K_2HPO_4	DMF	62	<5	11
9	Na_2CO_3	DMF	35	<5	<5
10	Et_3N	DMF	11	5	0
11	K_2HPO_4	DMA	71	<5	5
12[e]	K_2HPO_4	DMA	71	<5	7
13[f]	K_2HPO_4	DMA	71(67)	<5	6
14[f]	—[g]	DMA	31	19	11
15[h]	K_2HPO_4	DMA	55	<5	0

[a] Conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), *fac*-$Ir(ppy)_3$ (2 mol%) and base (1.0 equiv.) in solvent (2.0 mL) at 25 °C under the irradiation of 12 W blue LEDs for 12 h. [b] NMR yield with CH_2Br_2 as an internal standard. Isolated yields are indicated in parentheses. [c] Without *fac*-$Ir(ppy)_3$. [d] Reaction in the absence of light irradiation. [e] H_2O (0.5 equiv.) was added. [f] Reaction time: 3 h. [g] Without base. [h] α-Chloroacetophenone instead of **2a**.

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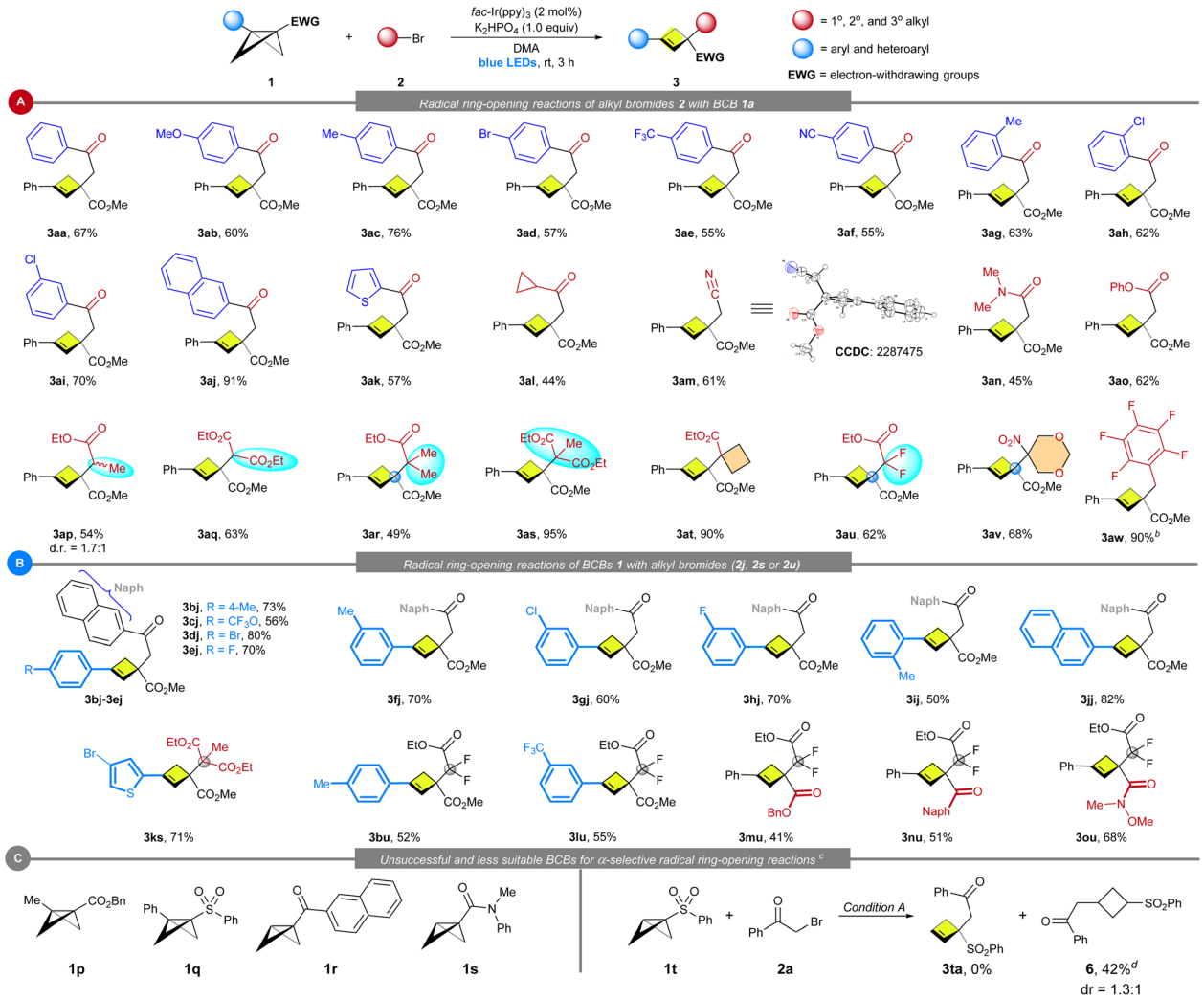
Further improvement of the yield was achieved with dimethylacetamide (DMA) instead of DMF as the solvent (entry 11). Notably, the ring-opening reaction can tolerate H_2O (entry 12). Only a 3-h reaction time was needed to reach >99% conversion (entry 13). In the absence of a base, the reaction yield was reduced from 71 to 31% (entry 14). Rather than alkyl bromide **2a**, α-chloroacetophenone was also competent to afford the product, albeit with a lower yield (entry 15).

With optimized reaction conditions established, we tested a range of different alkyl bromides (Scheme 2A). The reaction of bromoacetophenones with different substituents on the aryl ring, including electron-donating (4-OMe as in **3ab**) and electron-withdrawing groups (4-CF_3 as in **3ae**; 4-CN as in **3af**), at either the *para*, *meta*, or *ortho* position, also proceeded with good efficiency (**3aa–3ai**). The naphthyl-containing α-bromo ketone **2j** furnished **3aj** in 91% yield. Additionally, heterocyclic α-bromo ketone **2k** underwent the reaction smoothly to deliver the products in moderate yield (**3ak**). Aside from aromatic ketones, alkyl ketone **2l** containing a cyclopropyl group, can be smoothly transformed into the corresponding product **3al**. α-Carbonyl alkyl bromides bearing cyano (**2m**),[19] amide (**2n**) and ester (**2o**) groups are also suitable substrates. Besides primary alkyl bromides, secondary alkyl bromides are still maintaining decent yields (**3ap–3aq**). Photoredox catalysis has recently demonstrated potential for the construction of congested all-carbon quaternary centers *via* highly reactive radicals.[18] However, intermolecular construction of two contiguous all-carbon quaternary centers by visible light-induced photoredox catalysis remains underdeveloped.[18p] To our delight, tertiary-α-bromoalkyl esters (**2r–2t**) successfully afforded the corresponding congested cyclobutenes (**3ar–3at**) in 49–95% yields with exclusive α-selectivity. Importantly, ethyl bromodifluoroacetate also had high reactivity and delivered product **3au** bearing a *gem*-difluoromethylene (CF_2) group, which is popular



Scheme 2 Substrate scope investigation.[a] [a] Unless otherwise noted, reactions were performed with **1** (0.2 mmol), **2** (0.30 mmol), *fac*-Ir(ppy)$_3$ (2 mol%), K_2HPO_4 (1.0 equiv.), and DMA (2.0 mL), at room temperature under irradiation with 12 W blue LEDs for 3 h (condition A). Isolated yields are indicated. [b] Condition B: **1** (0.2 mmol)), **2** (0.30 mmol), *fac*-Ir(ppy)$_3$ (2 mol%), Na_2CO_3 (1.0 equiv.), Et_3N (0.1 equiv.), and DMF (2.0 mL), at room temperature under irradiation with 12 W blue LEDs for 12 h. [c] The ring-opening reactions of BCBs (**1p–1t**) with α-bromo ketone **2a** were conducted using condition A. [d] Combined isolated yield of the diastereomers.

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in drugs and in agrochemicals. Furthermore, tertiary-alkyl bromide **2v** with a nitro group smoothly reacted with **1a** and gave the product **3av** in reasonable yield. Besides α-carbonyl alkyl bromides, less-reactive benzyl bromide derivative **2w** was also a suitable substrate in the presence of *fac*-Ir(ppy)$_3$ as the photocatalyst under reoptimized condition B.

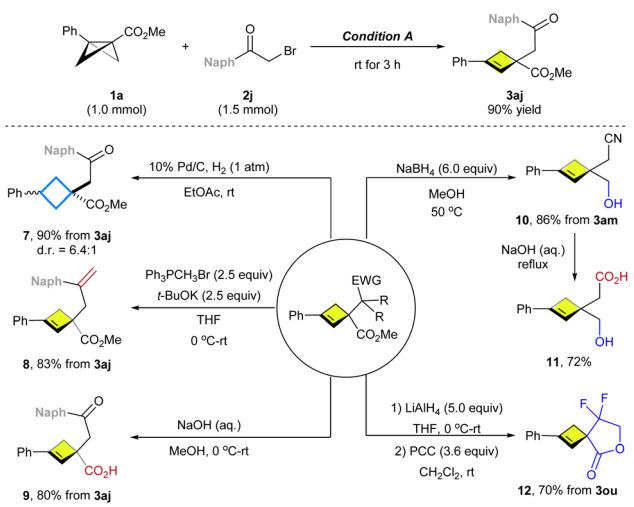
The scope and generality of this α-selective ring-opening in terms of 1,3-disubstituted BCBs with representative alkyl bromides (**2j**, **2s** and **2u**) is summarized in Scheme 2B. This method is amenable to a series of BCBs bearing different aromatic substituents, including alkyl (**1b**, **1f** & **1i**), CF_3O (**1c**), halogen (**1d**, **1e**, **1g** & **1h**) and CF_3 (**1l**) groups at the *para*-, *meta*- or *ortho*-position of aryl rings, and led to the corresponding cyclobutenes in moderate to excellent yields (50–80%). Both naphthyl (**1j**) and thienyl (**1k**) substituted BCBs reacted smoothly under condition A. Apart from BCB esters (**1b–1m**), both BCB ketone **1n** and Weinreb amide derived BCB **1o** were compatible, giving the corresponding ring-opening products bearing two contiguous quaternary centers and CF_2 groups in synthetically useful yield (**1n** + **2u** → **3nu**; **1o** + **2u** → **3ou**). The reaction is not limited to aryl-substituted BCBs. Alkyl-substituted BCB **1p** was also found to be compatible, albeit with a low yield (5% NMR yield) under conditions A (for more details, see ESI Scheme S1†). 1,3-Disubstituted sulfonyl BCB **1q** did not furnish the desired cyclobutene product. Additionally, we investigated the influence of the substituent at the β-position of BCB in this site-selective reaction. Although the ring-opening reaction of monosubstituted BCB ketone **1r** (or BCB amide **1s**) results in a complex mixture, the reaction of monosubstituted BCB sulfone **1t** with **2a** produces the cyclobutane product **6** through β-addition (Scheme 2C).

To explore synthetic transformations of these functionalized cyclobutenes, a scale-up synthesis of **3aj** (1.0 mmol) was performed without any loss in efficiency and selectivity (Scheme 3). The double bond in **3aj** was hydrogenated over Pd/C to produce trisubstituted cyclobutane **7** in 90% yield. The ketone group in **3aj** was converted into an alkene in **8**. Hydrolysis of the ester group of **3aj** afforded the free carboxylic acid **9**. Moreover, reduction of the ester group in **3am** using $NaBH_4$ provided the primary alcohol **10** in 86% yield. Also, functionalized cyclobutene **11** was synthesized from **10** by hydrolysis of the nitrile under basic conditions. Of note, reduction of the Weinreb amide **3ou** with $LiAlH_4$ followed by oxidation allowed for the construction of spirolactone **12** containing a 4-membered ring.

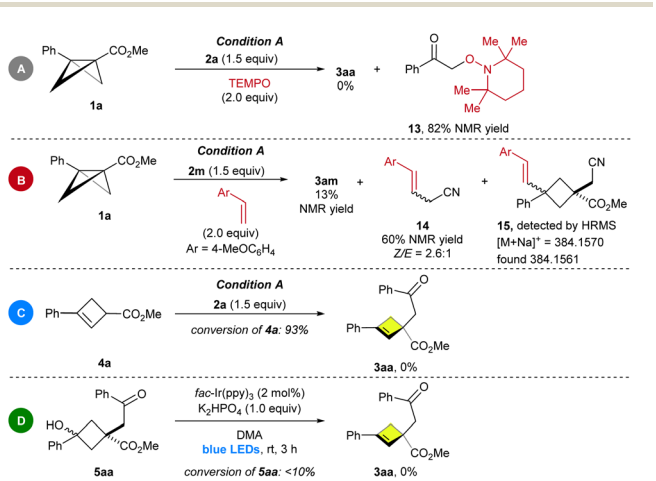
To rationalize the reaction pathway, some experiments were designed and performed. First, the reaction was completely shut down in the presence of TEMPO. In the meantime, the radical trapping product **13** was obtained in 82% yield (Scheme 4A). Second, the reaction of 2-bromoacetonitrile with **1a** and 4-methoxystyrene was attempted under condition A, and the cyclobutene **3am** together with **14** and **15** was detected by ^{1}H NMR and HRMS, indicating that the reaction proceeds *via* a radical pathway with α-selectivity (Scheme 4B). Subsequently, the treatment of **4a** with **2a** under the standard reaction conditions did not furnish the aimed **3aa** (Scheme 4C). This result demonstrated that the reaction was not proceeding *via* the cyclobutene intermediate **4a**. In addition, as shown in Scheme 4D, when **5aa** was treated with the photocatalyst under optimized conditions, no desired product was observed.

Moreover, the light–dark experiment was performed using alternative intervals of light and dark (Scheme 5). It has been demonstrated that this photochemical transformation necessitates continuous exposure to visible light, indicating that chain propagation may not be the primary reaction pathway. A Stern–Volmer plot showed strong quenching of *fac*-Ir(ppy)$_3$ ($E^{IV/III*} = -1.84$ V *vs.* SCE) by alkyl bromide **2a** ($E_{ox} > 1.6$ V *vs.* SCE, $E_{red} = -1.2$ V *vs.* SCE),[18q] favoring an oxidative quenching cycle (Scheme 6 and Fig. S2–S4, in the ESI†).

Based on these preliminary results, a reasonable mechanistic rationale for our photoredox transformation was formulated, as shown in Scheme 7. Upon photoexcitation, the photocatalyst *fac*-Ir(ppy)$_3$ is converted into the strongly reducing excited state Ir(III)*, which is capable of reducing an alkyl halide **2** to its corresponding alkyl radical **INT-A** and generating Ir(IV). Upon α-selective radical addition of the electrophilic species **INT-A** to BCB **2**, the key C–C bond formation step occurred, thus



Scheme 3 Scale-up synthesis and synthetic transformations.



Scheme 4 Control experiments.

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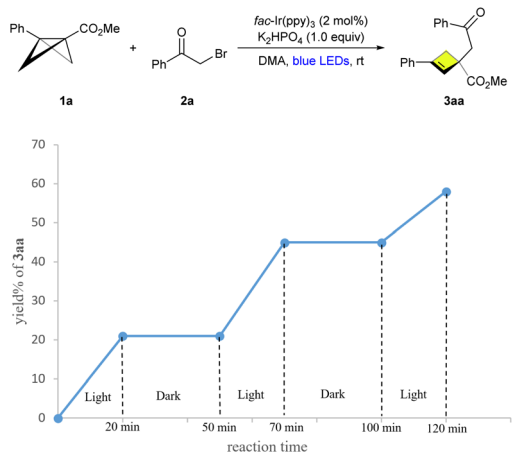
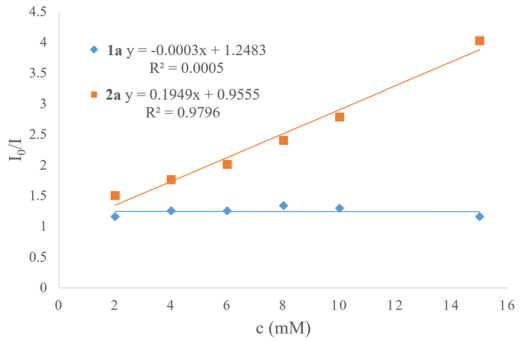
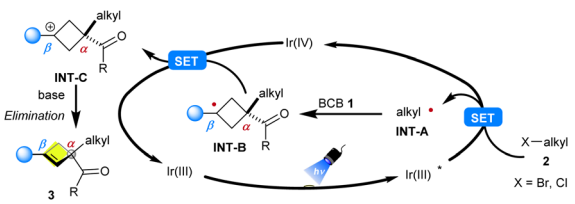


Scheme 5 Light on/off experiment.



Scheme 6 Stern–Volmer plots of *fac*-Ir(ppy)$_3$ with different quenchers (**1a** or **2a**).



Scheme 7 Proposed mechanism.

forming the more stable tertiary radical **INT-B**. Then, **INT-B** undergoes a single-electron oxidation with Ir(IV) to form the carbocation **INT-C** with the regeneration of the photocatalyst. Finally, the cyclobutene **3** can be formed through an elimination reaction with the assistance of a base.

Conclusion

In summary, we report the first use of ring-opening reactions of 1,3-disubstituted bicyclobutanes with alkyl radical precursors to construct cyclobutenes *via* visible light-induced photoredox catalysis. This study provides a concise and modular method for the synthesis of highly valuable alkylated cyclobutenes. A broad range of alkyl halides including 1°, 2°, and 3° alkyl bromides can be coupled under mild reaction conditions to afford 1,1,3-trisubstituted cyclobutenes with a single all-carbon quaternary center, or with two contiguous (all-carbon quaternary) centers. The synthetic utility of the reaction was showcased by several transformations. Notably, unlike the β-selectivity disclosed in classical polar and radical strain-release reactions of BCBs, an exclusive α-selectivity in current radical ring-openings of acyl-BCBs with carbon-centered radicals is obtained, which is complementary to Aggarwal's α-selective ring-opening reactions of monosubstituted BCB-Bpin with heteroatom-centred polar nucleophiles.[13a]

Data availability

All detailed procedures, characterization data and NMR spectra are available in the ESI.†

Author contributions

Y. X., T.-T. X., J.-L. Z., F. W., L. T., and R.-Y. L. performed the experiments and conducted the analytical characterization. W.-B. W. 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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