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Copper-catalyzed radical cascade reaction of simple cyclobutanes: synthesis of highly functionalized cyclobutene derivatives†

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Cyclobutenes as versatile and highly valuable synthons have been widely applied in synthesis. Although various methods for their synthesis have been well established, new strategies for the construction of the cyclobutene skeleton from simple substrates are still highly desirable. Starting from simple cyclobutanes, the construction of the cyclobutene skeleton especially introducing multiple functional groups simultaneously had never been achieved. Here, we developed a novel radical cascade strategy for the synthesis of highly functionalized cyclobutenes directly from cyclobutanes involving rare cleavage of four or five C–H bonds and formation of two C–N/C–S or three C–Br bonds. With copper as catalyst and *N*-fluorobenzenesulfonimide (NFSI) as oxidant, a wide range of diaminated, disulfonylated and tribrominated cyclobutene derivatives were efficiently synthesized.

Introduction

Cyclobutenes are versatile and highly valuable building blocks for organic synthesis¹ and widely exist as essential structural units in diverse natural products.² Therefore, the synthesis of these compounds has been the focus of intensive research, resulting in numerous methods. The typical [2 + 2] cycloaddition between an alkyne and an alkene^{3–5} is still attractive. Nevertheless, electron balance between the two coupling partners was always necessitated (Scheme 1a). Other methods such as 4 π -electrocyclization of conjugated dienes or vinyl-allenes,⁶ and cycloisomerization reactions of enynes or ene-allenyl compounds⁷ are effective for the construction of the cyclobutene skeleton. While most of these methods are suitable for methylenecyclobutenes or cyclobutene-fused cyclic compounds. Recently, the Maulide group⁸ reported an intriguing study that employed a highly active cyclobutene-fused lactone as the key intermediate undergoing a nucleophilic ring-opening process to successfully synthesize a series of functionalized cyclobutene carboxylic acid derivatives (Scheme 1b). Although the methods described above have led to great achievements for the construction of cyclobutenes, new strategies for accessing the cyclobutene skeleton from simple

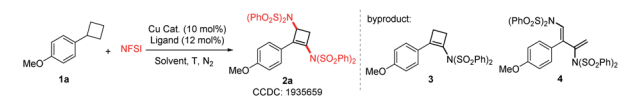
substrates along with introducing multiple external functional groups are highly desirable but very rare.

Cyclobutanes are a class of important organic synthesis intermediates widely used in various important organic transformations and total synthesis of natural products.⁹ According to retrosynthetic analysis, if a cyclobutane could undergo dehydrogenation and multiple C–H functionalizations, a highly functionalized cyclobutene might be assembled. There are some examples of the formation of the cyclobutene framework from cyclobutane derivatives (chloro-/bromo-cyclobutane, cyclobutanol, or cyclobutylsulfonate) *via* elimination reaction.¹⁰ However, so far, to the best of our knowledge, the synthesis of highly functionalized cyclobutene derivatives directly from simple cyclobutanes has never been realized. We recognized that this assumption faces three arduous challenges: (1) a relatively higher ring strain energy of cyclobutene compared with cyclobutane (*ca.* 30.2 kcal mol^{−1} *vs.* *ca.* 26.3 kcal mol^{−1});¹¹ (2) high bond dissociation energy (*ca.* 100.5 kcal mol^{−1}) of the cyclobutane C–H bond;¹² (3) highly selective hydrogen atom abstraction of several sp³ C–H bonds in cyclobutanes. With the vigorous renaissance of radical chemistry, radical cascade reactions have been employed as a powerful strategy for rapidly accessing complex molecules in one step under mild conditions.¹³ We supposed that multiple sp³ C–H bond radical hydrogen abstraction functionalization cascade reactions might be efficient for the synthesis of multiple functionalized cyclobutene derivatives directly from cyclobutanes. Considering our continuous interest in C–H functionalization *via* direct hydrogen atom abstraction,¹⁴ *N*-centered radical chemistry,¹⁵ and radical asymmetric ring-opening of small ring compounds,¹⁶ herein, with copper as a catalyst and *N*-fluorobenzenesulfonimide (NFSI) as an oxidant

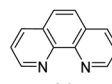
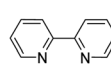
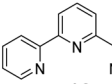
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Table 1 The optimization of reaction conditions of 1,3-diaminocyclobutene synthesis^a


Entry	Cu cat.	Ligand	Solvent	T (°C)	2a yield (%)
1 ^b	CuBr	L1	CH ₃ CN	50	15
2	CuBr	L2	CH ₃ CN	50	8
3	CuBr	L3	CH ₃ CN	50	16
4 ^c	CuBr	None	CH ₃ CN	50	86
5	CuBr	None	CH ₃ CN	40	93
6	CuBr ₂	None	CH ₃ CN	40	51
7	CuCl	None	CH ₃ CN	40	65
8	CuOAc	None	CH ₃ CN	40	44
9	Cu ^d	None	CH ₃ CN	40	45
10	CuBr	None	DCM	40	0
11	CuBr	None	DCE	40	0
12	CuBr	None	THF	40	Trace
13	CuBr	None	PhCF ₃	40	0
14	CuBr	None	CH ₃ CN	30	75
15 ^e	CuBr	None	CH ₃ CN	40	77
16 ^f	CuBr	None	CH ₃ CN	40	93
17 ^g	CuBr	None	CH ₃ CN	40	76

^a Reaction conditions: **1a** (0.2 mmol), NFSI (3 equiv.), Cu cat. (10 mol%), solvent (2 mL), N₂, 4 h. Yields were determined by ¹H NMR of the crude mixture with CH₂Br₂ as an internal standard. ^b **3** and **4** were obtained in 6% and 5% yields, respectively. ^c A trace amount of **3** was observed and a very small amount of **4** (6%) was detected. ^d Cu(CH₃CN)₄PF₆ was used as the catalyst. ^e NFSI (2.5 equiv.). ^f CuBr (5 mol%). ^g CuBr (2 mol%).

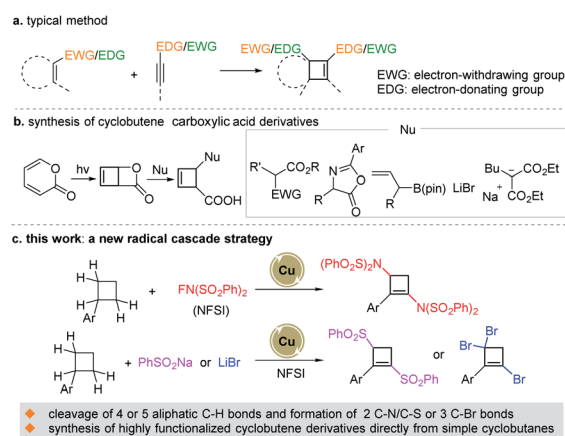
and nitrogen source, an efficient method for the synthesis of 1,3-diaminocyclobutene derivatives from cyclobutanes *via* a radical cascade process was developed. Furthermore, the Cu catalyst/NFSI system was successfully applied to synthesize 1,3-disulfonyl- or 1,3,3-tribromocyclobutene derivatives (Scheme 1c). These transformations involved the highly selective cleavage of four or five C–H bonds and the formation of two C–N/C–S or three C–Br bonds, straightforwardly synthesizing a series of highly functionalized cyclobutene derivatives, which cannot be accessed *via* known methods.

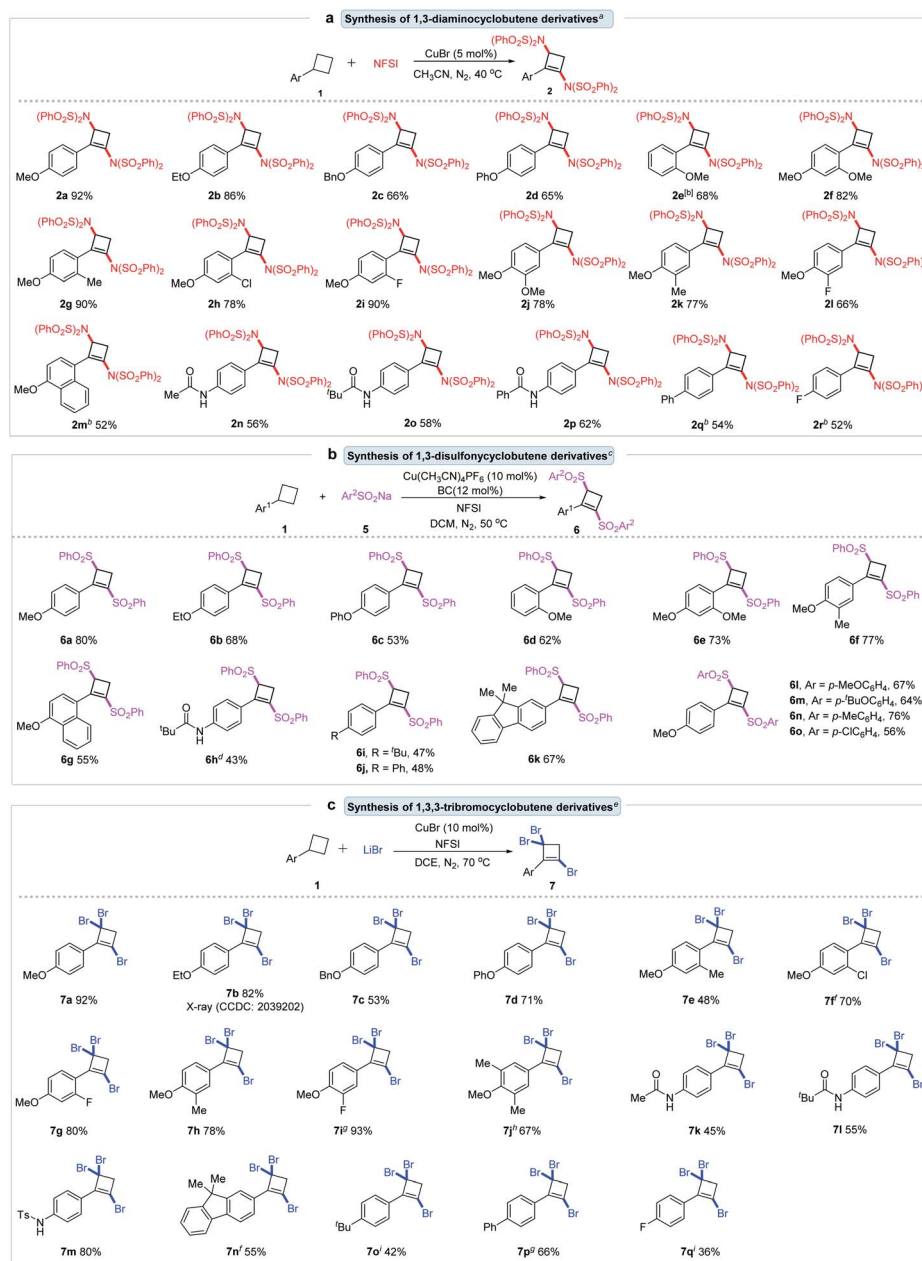
Results and discussion

In our previous work, by utilizing a copper catalyst/NFSI system, efficient hydrogen atom abstraction and radical amination could be realized.^{14a,b,15c–i,16} Therefore, in our initial research, we chose the reaction of arylcyclobutane **1a** with NFSI in the presence of a Cu catalyst as the model reaction to optimize the reaction conditions. After the reaction was performed at 50 °C for 4 h using 10 mol% CuBr as the catalyst and 12 mol% phen (**L1**) as the ligand, we found that 1,3-diaminocyclobutene **2a** was obtained in 15% yield, along with the formation of 1-

aminocyclobutene **3** (6%) and *E*-1,3-diamino-1,3-diene **4** (5%) (Table 1, entry 1). Viewing this result, we thought that **3** might be an intermediate for the formation of **2a**, and **4** should be generated from **2a** *via* a retro-4π-electrocyclization. Therefore, **2a** was treated with current conditions, giving **4** in 60% yield. Transformation of **3** was also conducted under the same conditions, and 60% **2a** and 23% **4** were obtained, respectively. Next, some experimental parameters were carefully screened (for details, see ESI Table S1†). Interestingly, in the absence of the ligand, the yield of **2a** was improved considerably (from 15% to 86%), and only a trace amount of **3** and a very small amount of **4** (5%) were detected (Table 1, entry 4). In order to further inhibit the retro-4π-electrocyclization of **2a**, the reaction of **1a** and NFSI was conducted at a lower temperature (40 °C). Delightfully, **2a** was obtained in 93% yield (Table 1, entry 5). The structure of **2a** was unambiguously confirmed by X-ray single-crystal analysis. Notably, the reaction of **1a** and NFSI not only formed the cyclobutene skeleton but also installed two amino groups *via* cleavage of four aliphatic C–H bonds and construction of an sp² C–N bond and an sp³ C–N bond. Scanning other copper catalysts (Table 1, entries 6–9) and different solvents (Table 1, entries 10–13) showed that CuBr and CH₃CN were the optimal catalyst and the best solvent, respectively. A much lower reaction temperature (30 °C) could not improve the yield of **2a** (Table 1, entry 14). Decreasing the amount of NFSI resulted in a lower yield of **2a** (Table 1, entry 15). Satisfyingly, reducing the loading amount of CuBr to 5 mol% did not affect the yield of **2a** (Table 1, entries 16 and 17).

With the optimal reaction conditions, we began to assess the generality of the method by investigating the substrate scope of this copper-catalyzed reaction. Diverse arylcyclobutanes were examined, efficiently synthesizing an array of 1,3-diaminocyclobutene derivatives. As shown in Scheme 2a, *para*-MeO-, EtO-, BnO-, and PhO-substituted arylcyclobutanes **1a–1d** could be smoothly converted to the desired 1,3-diaminocyclobutenes **2a–2d** in good to excellent yields (65–92%). *Ortho*-MeO-substituted cyclobutane **1e** could also form the desired **2e** in 68% yield. *Para*-methoxyphenylcyclobutane derivatives bearing electron-donating or electron-withdrawing

**Scheme 1** Synthetic methods of cyclobutene derivatives.



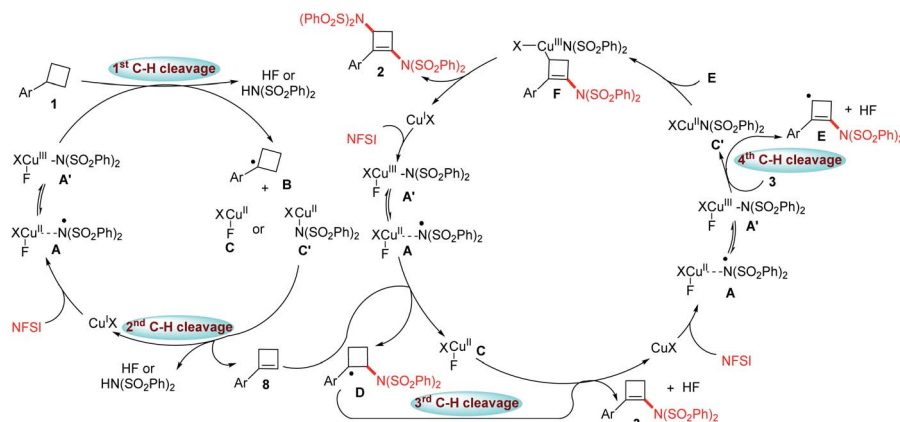
Scheme 2 Synthesis of highly functionalized cyclobutene derivatives directly from simple cyclobutanes. Reaction conditions: ^a **1** (0.2 mmol), NFSI (3 equiv.), CuBr (5 mol%), CH₃CN (2 mL) at 40 °C under N₂ for 4–9 h. ^b CuBr (10 mol%), Cu(CH₃CN)₄PF₆ (10 mol%), BC (2,9-dimethyl-4,7-diphenyl-1,10-phenanthroline, 12 mol%), DCM (6 mL) at 50 °C under N₂ for 20 h. ^c Ar₂SO₂Na (4.5 equiv.), 60 °C. ^d **1** (0.2 mmol), NFSI (4.3 equiv.), LiBr (3.3 equiv.), CuBr (10 mol%), DCE (2 mL) at 70 °C under N₂ for 4–9 h. ^e TMSBr (3.3 equiv.) instead of LiBr. ^f LiBr (4.0 equiv.), CuBr (5 mol%), 2,2':6',2''-terpyridine (6 mol%). ^g CuBr (5 mol%), 2,2':6',2''-terpyridine (6 mol%), 60 °C. ^h LiBr (4.0 equiv.). Yields of isolated products are reported.

groups such as MeO–, Me–, Cl–, and F– at the *ortho*- or *meta*-position of the benzene ring were competent substrates giving the corresponding **2f–2l** in 66–90% yields. 4-Methoxy-1-naphthyl substituted cyclobutane **1m** was effectively subjected to this reaction to produce 1,3-diaminocyclobutene **2m** in 52% yield. Notably, the amido moiety worked well and delivered the expected **2n–2p** in good yields. In addition, *para*-Ph and -F substituted benzylcyclobutanes **1q** and **1r** were also found to be tolerated in this transformation and formed the desired 1,3-

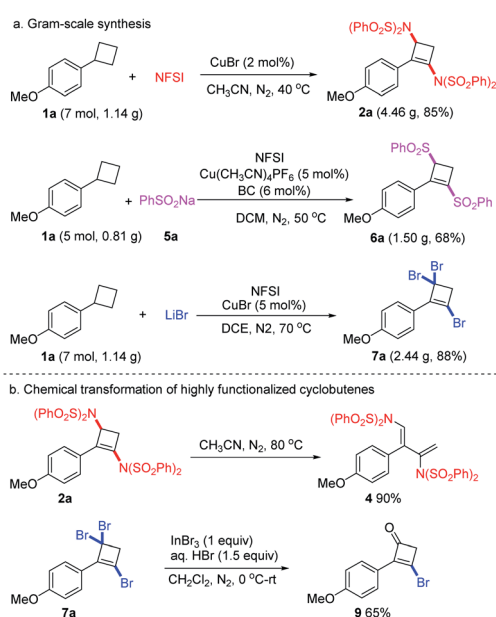
diaminocyclobutenes **2q** and **2r** with good efficiency. Alkyl substituted cyclobutanes, such as benzylcyclobutane and bromomethylcyclobutane, were ineffective.

The sulfonyl group is a core unit of many natural products and pharmaceuticals, and the sulfonyl compounds have shown important biologically active properties.¹⁷ Based on the achieved synthesis of diamino-substituted cyclobutenes from arylcyclobutanes, we turned to synthesize disulfonyl-substituted cyclobutene derivatives. When sodium phenylsulfite (**5a**) was





Scheme 3 Proposed reaction mechanism.



Scheme 4 Gram-scale synthesis and application of the new method.

added to the solution of **1a** in CH_3CN in the presence of CuBr (10 mol%), phen (12 mol%) and NFSI (3.5 equiv.), the desired 1,3-disulfonylbutene **6a** was obtained in 6% yield (Table S2, entry 1†). After carefully screening the reaction conditions, **6a** could be obtained in 80% yield (for details, see ESI Table S2†). As summarized in Scheme 2b, alkoxy or phenoxy substituted arylcyclobutenes could react well with **5a** to form the corresponding 1,3-disulfonylcyclobutenes **6a–6g** in good yields. An acylamino-substituted arylcyclobutane is a suitable substrate, leading to **6h** in acceptable yield. Tertiary butyl- and phenyl-substituted arylcyclobutenes, and 1-fluorenylcyclobutane worked smoothly under the reaction conditions to afford the disulfonylcyclobutenes **6i–6k** in 47–67% yields. Other sulfites were also examined. Arylsulfites bearing both electron-donating groups, such as methoxy, tertiary butyl and methyl, and electron-withdrawing groups, such as chloride, were well tolerated in this reaction, providing corresponding 1,3-

disulfonylcyclobutene derivatives **6l–6o** in 56–76% yields. Alkyl sulfites, such as sodium methanesulfinate and sodium phenylmethanesulfinate failed to undergo this reaction.

This novel cascade strategy was further employed to synthesize brominated cyclobutene derivatives from cyclobutenes. When the reaction of **1a** (0.2 mmol) and 2.5 equivalents of LiBr was performed in DEC (2 mL) in the presence of NFSI (3.5 equiv.) and CuBr (10 mmol%) at 50 °C for 4 h, surprisingly, 1,3,3-tribromocyclobutene **7a** was obtained in 48% yield (see ESI Table S3, entry 1†). Remarkably, unlike the above diamination and disulfonylation, this bromination reaction involved cleavage of five aliphatic C–H bonds and formation of three C–Br bonds. The geminal dibromo unit as a potential carbonyl group provides a good opportunity for further chemical transformations. After carefully optimizing reaction conditions, **7a** could be obtained in 92% yield (for details, see ESI Table S3†). Scheme 2c presents the scope of arylcyclobutenes for directly synthesizing a series of 1,3,3-tribromocyclobutenes. Various substituted arylcyclobutenes could react smoothly to provide the expected 2-aryl-1,3,3-tribromocyclobutenes in 36–93% yields. For example, arylcyclobutenes with an alkoxy (**1a–1c**) or phenoxy (**1d**) group at the *para*-position could undergo the bromination reaction, forming the desired **7a–7d** in good to excellent yields. The single-crystal of **7b** further supported the structure of the 1,3,3-tribromocyclobutene. 2/3-Substituted-4-methoxy phenylcyclobutenes could efficiently transform to the corresponding 1,3,3-tribromocyclobutenes **7e–7i** in 48–93% yields. The reaction of 3,5-dimethyl-4-methoxycyclobutane could smoothly occur, providing 1,3,3-tribromocyclobutene **7j** in good yield. Besides oxygen-containing groups, other groups, such as acylamido, 2-fluorenyl, tertiary butyl, biphenyl and fluorine, were compatible during this reaction, affording the corresponding **7k–7q** in 36–80% yields.

To understand the reaction mechanism, some controlling experiments were conducted. The addition of 2,6-di-*tert*-butyl-4-methylphenol (BHT) or 2,2,6,6-tetramethylpiperidinoxy (TEMPO) was found to completely inhibit the formation of **2a**. These results suggested that the reaction might involve radical intermediates. Since 1-aminocyclobutene **3** has been detected



and could further transform to **2a** and **4** (see conditions optimization of 1,3-diaminocyclobutene synthesis), we hypothesized that the cyclobutane might firstly form a cyclobutene. Then, the prepared cyclobutene **8a** was treated with NFSI under standard conditions, furnishing **2a** in 28% yield, which supported the existence of the cyclobutene intermediate. Combining all above experimental results and previous work,^{14,15c-h,16,18} we proposed a possible reaction mechanism. As depicted in Scheme 3, initially, the oxidation of Cu^I and NFSI formed Cu^{II}-coordinated nitrogen-centered radical species **A** or Cu^{III} species **A'**.

A' selectively abstracted the benzylic hydrogen atom from cyclobutane **1** to form benzylic radical **B** followed by β -H elimination to produce cyclobutene **8**. Alternatively, **B** might rebound with Cu^{II} species to generate Cu^{III} species followed by β -Cu-H elimination to generate **8**.¹⁹ Subsequently, the addition of N-centered radical **A** to **8** and β -H elimination afforded 1-aminocyclobutene derivative **3**. Then, the highly regioselective allylic hydrogen atom abstraction formed allylic radical **E** and Cu^{II}-N species **C'**. The combination of **C'** and **E** resulted in Cu^{III} species **F**, which underwent a reductive elimination to afford 1,3-diaminocyclobutene **2**, along with the regeneration of the Cu^I catalyst. The probable mechanisms for the formation of 1,3-disulfonylcyclobutene **6** and 1,3,3-tribromocyclobutene **7** are discussed in the ESI (see Fig. S1 and S2†). As shown in Scheme 3, the catalytic system of Cu and NFSI is very interesting, and it supports an efficient radical cascade process involving benzylic hydrogen atom abstraction, β -H elimination, radical addition, and allylic hydrogen atom abstraction/functionalization. It might open a new window for designing useful radical cascade reactions of multiple sp³ C-H bonds.

A gram-scale synthesis was carried out to demonstrate the practicability, and the target 1,3-diaminocyclobutene **2a**, 1,3-disulfonylcyclobutene **6a** and 1,3,3-tribromocyclobutene **7a** were obtained in 85%, 68%, and 88% yields, without significant loss of efficiency (Scheme 4a). We also briefly investigated further transformation of these multi-substituted cyclobutenes (Scheme 4b). 1,3-Diaminocyclobutene **2a** could smoothly undergo retro-4 π -electrocyclization²⁰ at 80 °C to stereospecifically furnish *E*-1,3-diaminodiene **4** in excellent yield.²¹ Additionally, the geminal dibromo unit of 1,3,3-tribromocyclobutene **7a** could efficiently transfer into the carbonyl group in the presence of InBr₃/HBr to afford cyclobutenone **9** in good yield.²²

Conclusions

In conclusion, we have developed an unprecedented copper-catalyzed highly efficient radical cascade reaction of simple cyclobutenes, straightforwardly synthesizing diverse 1,3-diaminocyclobutenes, 1,3-disulfonylcyclobutenes, and 1,3,3-tribromocyclobutenes under mild conditions in good yields. This methodology provides the first synthesis of cyclobutene derivatives directly from cyclobutenes along with simultaneously introducing multiple external functional groups. Mechanism study showed that this novel radical cascade transformation might involve cleavage of four or five C-H bonds. Further

application for the construction of diverse functionalized cyclobutenes is underway.

Data availability

All experimental and characterization data in this article are available in the ESI.† Crystallographic data for compounds **2a** and **7b** have been deposited in the Cambridge Crystallographic Data Centre (CCDC) under accession number CCDC 1935659 (**2a**) and CCDC 2039202 (**7b**).

Author contributions

Y. Li and Q. Zhang directed the investigations. C. Liu, Y. Li and Q. Zhang prepared the manuscript. C. Liu performed the synthetic experiments and analysed the experimental data. X. Shangguan double-checked the data in the ESI. All authors contributed to the writing of this paper.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

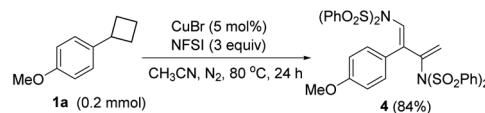
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