# Photoredox Catalyzed Strain-Release Driven Synthesis of Functionalized Spirocyclobutyl Oxindoles

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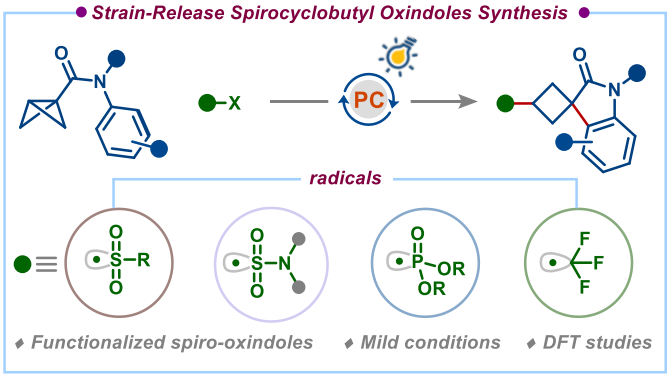
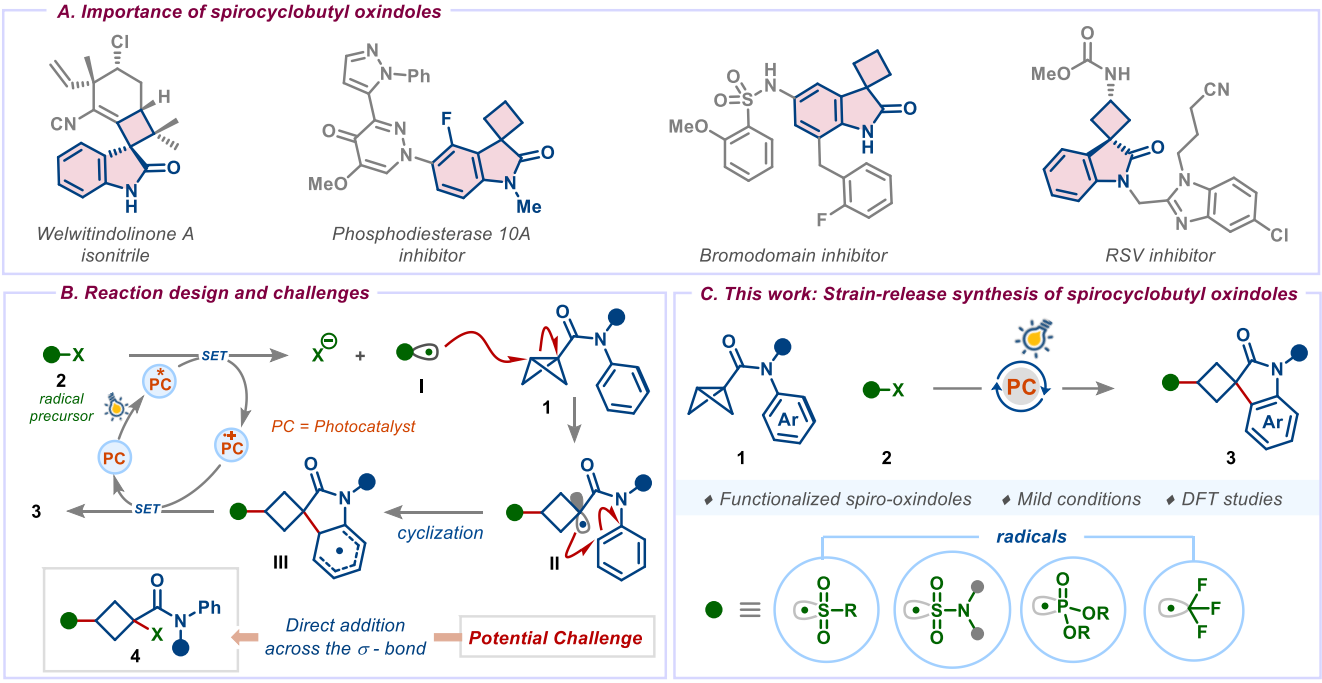



**ABSTRACT:** Spirocyclobutyl oxindoles have garnered substantial attention in drug discovery and pharmaceuticals owing to their wide range of biological activities. Strain-release in small-ring compounds is a powerful strategy to enable efficient access to complex molecules. In this study, we have successfully realized a photoredox-catalyzed strain-release radical spirocyclization approach to attain functionalized spirocyclobutyl oxindoles. A diverse array of radicals, such as sulfonyl, phosphonyl, and trifluoromethyl were added efficiently to the strained C-C σ bond of bicyclobutanes (BCBs) to afford a library of spirocyclobutyl oxindoles. Furthermore, the obtained products could be transformed into valuable building blocks. The observed reactivity and selectivity have been rationalized based on density functional theory calculations.

Spirocyclic scaffolds have been recognized as potential pharmacophores in drug discovery and pharmaceuticals because of their unique and inherently rigid three-dimensional architecture.[1] The conformational rigidity ensures that substituents are positioned in a well-defined and highly predictable manner, facilitating vectorization and allowing efficient interactions of ligands with binding sites.[2] The precise control of three-dimensional structure by introducing a cyclobutane ring further improves various physicochemical and pharmacokinetic properties, including metabolic stability, lipophilicity, permeability, and acidity/basicity.[3] The identification of such advantageous factors has fueled a surge in the discovery of biologically active spirocyclobutanes.[1d, 4] Among these motifs, spirocyclobutyl oxindoles have drawn the immense interest of researchers in recent years not only due to their presence in natural products but also for their broad spectrum of biological activities including antifungal,[5] acting as phosphodiesterase inhibitor (for the treatment of Parkinson's),[6] bromodomain and RSV inhibitor (Scheme 1A).[5, 7] Despite these attractive features, there is a limited range of strategies available for the synthesis of spirocyclobutyl oxindoles.[8] Current approaches involve a metal-catalyzed C-H activation of benzocyclobutene,[9] dienamine-mediated [2 + 2]-cycloaddition,[10] or radical intramolecular cyclizations.[11] Another limitation is accessing heteroatom or fluorine pendant spirocyclobutyl oxindoles that would be amenable to additional structural diversification. Consequently, modular, catalytic, sustainable methods to access functionalized spirocyclobutyl oxindoles are highly desirable and would be valuable for discovering new bioactive compounds.

The strain-release in small organic molecules is an efficient tool that unlocks unique reactivities, allowing a library of useful synthetic transformations with applications in total synthesis, drug discovery, and bioconjugation.[12] Particularly, bicyclo[1.1.0]butane (BCB) derivatives have enormous synthetic potential and have gained considerable attention among synthetic chemists not only due to their unique structural features but also for their ability to give efficient access to synthetically challenging scaffolds at ambient conditions.[13] The strained C-C σ bond of BCB derivatives was reported to participate in various cycloadditions,[14] difunctionalizations,[15] carbene insertions,[16] ene-type,[17] and cascade reactions[18] under photochemical and Lewis-acid catalyzed conditions. In the past decade, photocatalytic strategies that depend on the ability of photocatalysts to absorb light and participate either in electron transfer or energy transfer processes with organic molecules have evolved as an efficient synthetic tool for chemical synthesis. Herein, we envisioned merging two main pillars of synthetic methodology-photoredox catalysis and strain release-to develop a new radical strategy that would give access to spirocyclobutyl oxindoles.




**Scheme 1:** A) Importance of spirocyclobutyl oxindoles. B) Reaction design and challenges. C) This work: Strain-release driven synthesis of spirocyclobutyl oxindoles.

We postulated that radical intermediate **I**, generated from the radical precursor **2** via a single-electron reduction by the excited-state photocatalyst, could add onto the strained C-C σ bond of BCB **1** to give electrophilic radical **II**. Subsequent cyclization onto the arene ring would lead to radical intermediate **III**. Finally, single-electron oxidation of **III** by the oxidized photocatalyst followed by deprotonation leads to the formation of the spirocyclobutyl oxindole **3** while completing the photocatalytic cycle (Scheme 1B). However, we identified a major issue associated with this hypothesis: the radical intermediate **II** could undergo direct addition before the cyclization to give the direct addition product **4**. Despite this challenge, here we report our success in developing a photoredox catalyzed radical spirocyclization strategy to access functionalized spirocyclobutyl oxindoles (Scheme 1C). The formation of the direct addition product was prevented by selecting a suitable radical precursor. Furthermore, we have successfully added trifluoromethyl and phosphonyl radicals to BCB-amides to access trifluoromethylated and phosphonylated spirocyclobutyl oxindoles. It is important to note that phosphoryl radicals have not been added to the strained C-C σ bond of BCB to date. Furthermore, the obtained products could be further transformed into valuable building blocks. DFT study has rationalized the observed reactivity and stereoselectivity outcomes.

Our initial investigations commenced with the use of 4-fluorobenzenesulfonyl chloride (**2a**) as a sulfonyl radical precursor. The irradiation of BCB **1a**, sulfonyl chloride **2a**, and 4-CzIPN photocatalyst in acetonitrile solvent yielded the desired spirocyclized oxindole product **3a** in 30% yield with *dr* 2:1, alongside the formation of the direct addition product **4a** in 30% yield (Fig. 1, column 1). The direct addition product **4a** could be formed via an atom transfer radical addition (ATRA) process (*vide infra*). To suppress the direct addition product, we sought an alternative sulfone radical precursor with a non-halogenic counterpart. Although the complete suppression of the direct addition product was achieved by employing *S*-phenyl 4-fluorobenzenesulfonothioate **2b**, the yield of the desired product was not improved (Fig. 1, column 2). Phenyl 4-fluorobenzenesulfonate (**2c**) and 2-((4-fluorophenyl)sulfonyl)isoindoline-1,3-dione (**2d**) did not provide the desired spirocyclobutyl oxindole product **3a** (Fig. 1, column 3-4). The lack of reactivity observed with **2c** could be due to its high reduction potential ($E_{1/2} = -2.03$ V vs. SCE of **2c**),[19] whereas the unreactivity of the radical precursor **2d** can be attributed to its poor solubility in acetonitrile. Next, our focus shifted towards employing *N*-(diphenylmethylene)-4-fluorobenzenesulfonamide (**2e**), previously used by the groups of Glorius,[20] Du,[20b] and Zhang[20c] for difunctionalization of olefins via energy transfer photocatalysis. We were pleased to find that the reaction with **2e** resulted in the exclusive formation of **3a**, providing the desired product in 85% yield (Fig. 1, column 5). These promising results encouraged us to further optimize the reaction conditions by employing tunable metal-based photocatalysts. Among the photocatalysts screened (Fig. 1, columns 6-10), $Ir(ppy)_3$ emerged as the best photocatalyst with the quantitative formation of the desired product **3a**. Control experiments demonstrated that both photocatalyst and light irradiation were essential for reactivity (Fig. 1, columns 11 and 12).

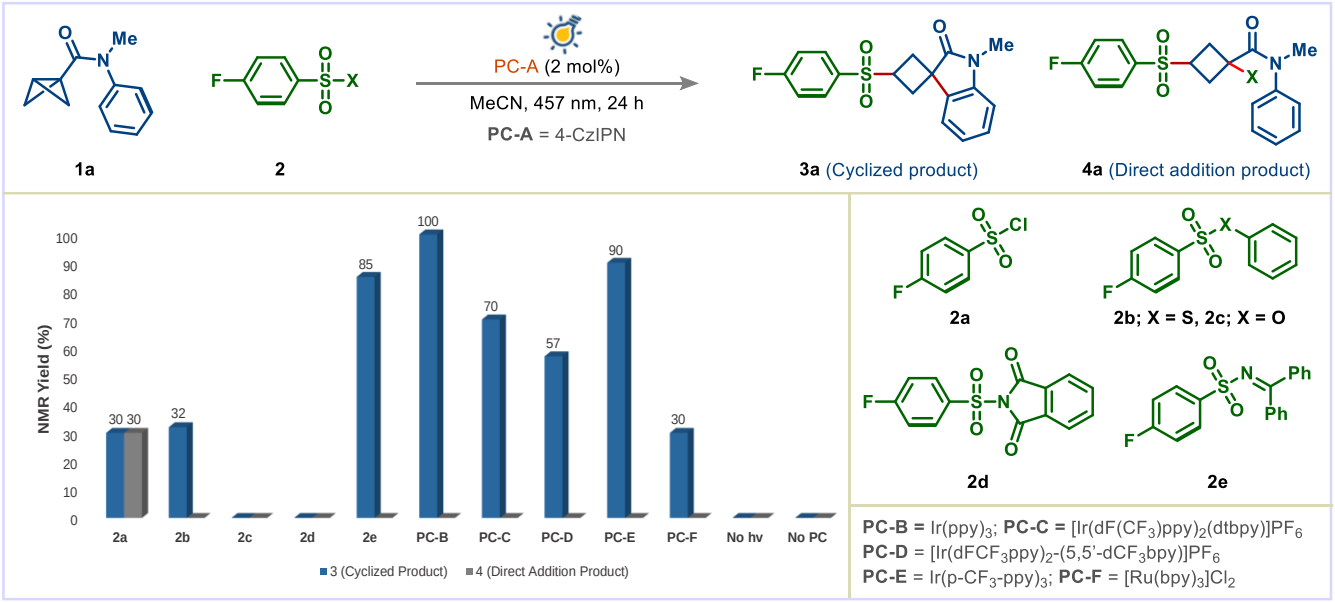
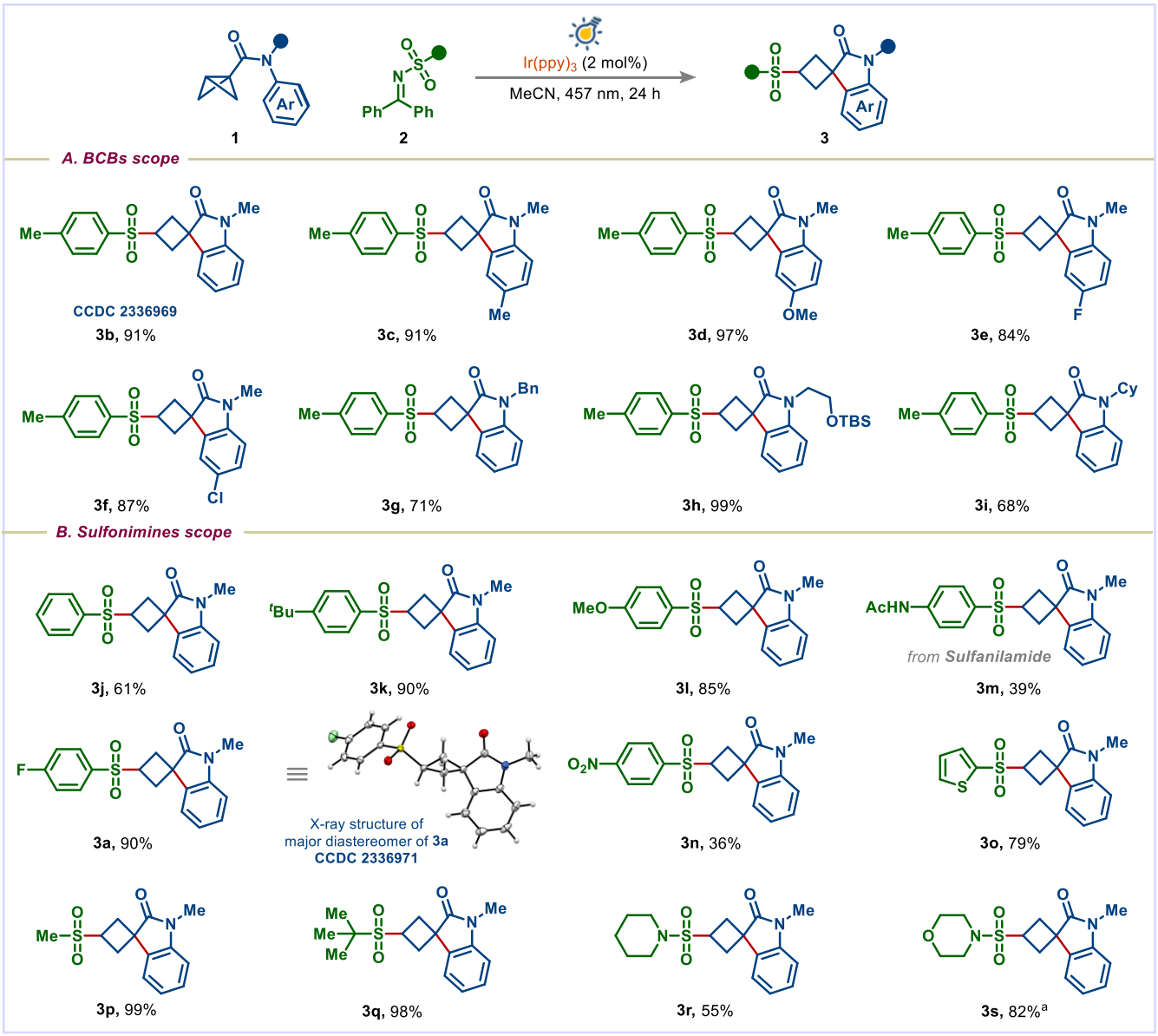



**Figure 1:** Optimization of reaction conditions. General Conditions: **1a** (0.1 mmol), **2** (1.0 equiv), MeCN (0.1 M) and PC (2 mol%), 457 nm, 24 h. Light source: Photocube. 4-CzIPN was used as a photocatalyst in columns 1-5. *dr* for **3a** is 2:1. Yields and *dr* were determined from crude reaction mixture by $^{19}$F-NMR using $PhCF_3$ as internal standard.

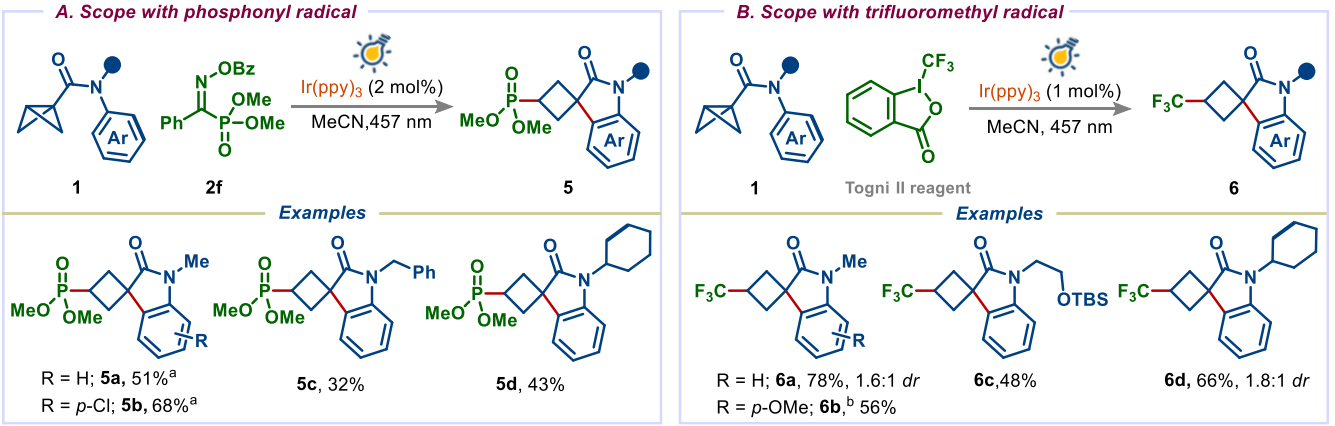
With the established optimal reaction conditions, we proceeded to evaluate the generality of this reaction with a broad range of BCB amides (Scheme 2A). BCB amide **1a** provided the spirocyclobutyl oxindole **3b** in 91% yield. The structure of minor diastereomer of **3b** was determined by X-ray analysis (CCDC 2336969). Various aryl rings in BCB amides bearing electron-donating substituents in the *para* position, such as methyl and methoxy, and electron-withdrawing substituents, such as fluoro and chloro groups, were well tolerated, providing the corresponding products **3c-3f** in good to excellent yields. BCBs with various substituents on nitrogen, including benzyl, $CH_2CH_2OTBS$, and cyclohexyl, underwent the desired transformation successfully, affording the products **3g-3i** in good yields. Subsequently, the scope and generality of the sulfone radical precursor **2** were investigated using BCB **1a** (Scheme 2B). Simple phenyl-sulfonimine and aryl-sulfonimines containing electron-donating groups, such as *p*-$^t$Bu, and *p*-OMe, were well participated in this reaction (products **3j-3l**). Sulfanilamide derivative could also be used as a sulfonyl radical precursor to access the spirocyclobutyl oxindole **3m** in 39% yield. Electron-deficient aryl-sulfonimines were also viable substrates in this reaction, giving the products **3a** (CCDC 2336971) and **3n**. Heterocyclic-sulfonimine, such as 2-thiophenyl was also found to be a suitable substrate in this reaction (product **3o**). Additionally, sulfone radicals bearing alkyl substituents were tolerated and furnished the corresponding spirocyclobutyl oxindoles **3p-3q** in high yields. Given the importance of sulfonamides in medicinal chemistry, we next investigated sulfonamide radical precursors. Piperidine and morpholine substituted sulfonyl radicals were successfully added to BCB **1a**, giving the products **3r-3s** in good yields.

Phosphorus-embedded scaffolds are omnipresent in several bioactive molecules and pharmaceuticals,[21] owing to their ability to regulate a wide range of cellular processes, including protein signaling,[22] gene expression,[23] and cellular metabolism.[24] Considering their multifunctional role, we were interested in incorporating phosphonate moiety into spirocyclobutyl oxindole. For this reason, we employed the radical precursor **2f**[25] in our strain-release method to enable the synthesis of C($sp^3$)−P(V) cyclobutane-containing spirooxindoles. When we subjected phosphonyl radical precursor **2f** to our standard conditions, we obtained the desired products **5a-5d** in moderate to good yields (Scheme 3A). To the best of our knowledge, there are no reports on the addition of phosphonyl radicals to the bicyclobutane system.

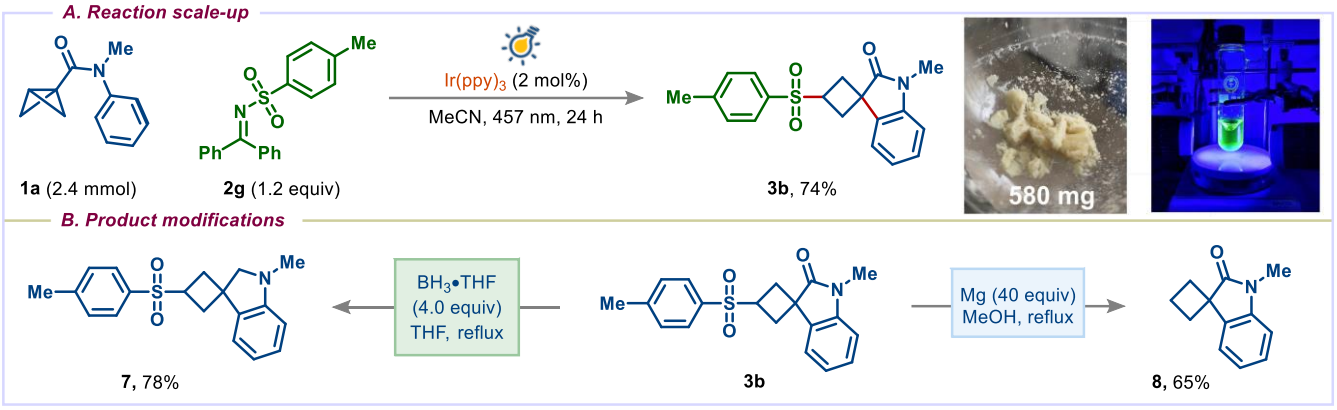
Incorporating fluorinated functionalities, particularly trifluoromethyl motif, into a therapeutic or diagnostic small molecule can enhance its pharmacokinetics and physicochemical properties.[26] Thus, the introduction of trifluoromethyl group onto spirocyclobutyl oxindoles could enhance their biological activities. Therefore, we turned our attention to the development of a trifluoromethylative cyclization cascade. Our initial attempts to replace sulfonimine with Togni II reagent under the standard conditions demonstrated that trifluoromethylation was indeed possible. However, the desired product was obtained with a moderate yield. A quick optimization (see the SI) improved the yield to 78%. Pleasingly, aryl and nitrogen-substituted BCBs successfully participated in this reaction, giving trifluoromethylated spirocyclobutyl oxindoles **6a-6d** in moderate to good yields (Scheme 3B).



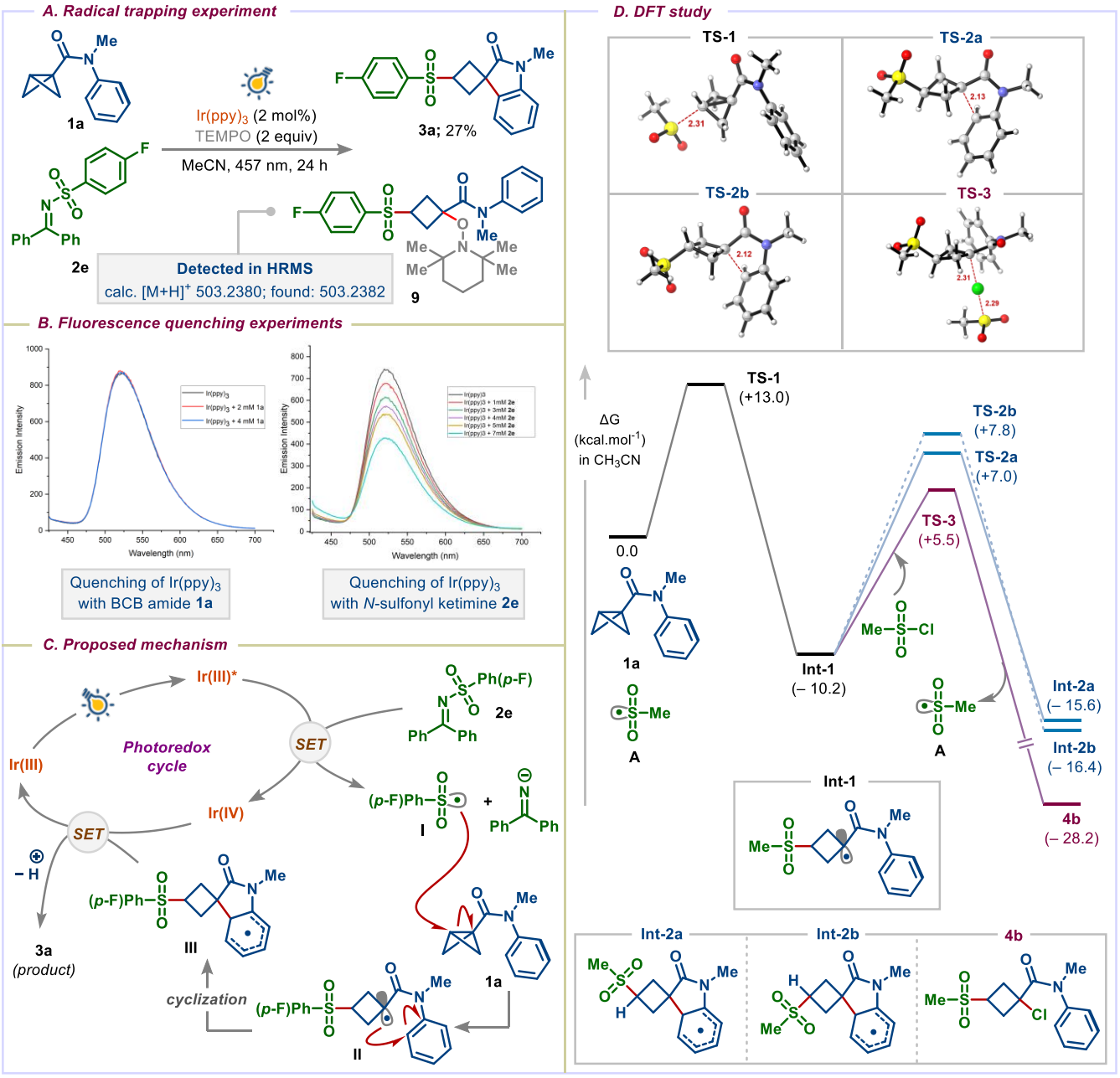

**Scheme 2:** Scope of the reaction with BCBs and sulfonyl radicals. Reaction conditions: **1** (0.3 mmol), **2** (1.2 equiv) and Ir(ppy)$_3$ (2 mol%) in MeCN (0.1 M), 457 nm, 24 h. Light source: Photocube. Yields are of isolated products and 2:1 *dr* was determined by $^1$H NMR from crude reaction mixture. [a]0.2 mmol scale.




**Scheme 3:** A) Scope with phosphonyl radical. Reaction conditions: **1** (0.3 mmol), **2f** (1.2 equiv) and Ir(ppy)$_3$ (2 mol%) in MeCN (0.1 M), 457 nm, 12 h. [a]0.2 mmol scale. B) Scope with trifluoromethyl radical. Reaction conditions: **1** (0.3 mmol), Togni II reagent (1.0 equiv) and Ir(ppy)$_3$ (1 mol%) in MeCN (0.05 M), 457 nm, 12 h. [b]0.15 mmol scale. Light source: Photocube. Yields are of isolated products and diastereomeric ratio was determined by $^1$H NMR from crude reaction mixture. Unless otherwise specified, diastereomeric ratio is 2:1.




**Scheme 4:** A) Reaction scale-up. B) Product modifications.




**Scheme 5:** A) Radical trapping experiment. B) Fluorescence quenching experiments. C) Plausible mechansim. D) DFT study: energy profile diagram.

To showcase the synthetic utility of our methodology, first, the spirocyclobutyl oxindole **3b** was synthesized in a 2.4 mmol scale with 74% yield (Scheme 4A). The obtained product **3b** could be efficiently converted to the spirocyclobutyl dihydroindole derivative **7**, another important motif in medicinal chemistry,[27] in 78% yield by treatment with borane. The sulfone group could be easily removed under reflux conditions using Mg in methanol to afford the product **8** in 65% yield (Scheme 4B).

We next turned our attention to the mechanism of the reaction. A radical trapping experiment was conducted to identify the key intermediates involved in the reaction. Performing the standard reaction with TEMPO diminished the yield of the reaction, along with the detection of TEMPO adduct **9**, supporting the radical intermediacy in the reaction (Scheme 5A). Fluorescence quenching experiments show that Ir-photocatalyst is quenched by sulfonimine **2e**, not by BCB **1a** (Scheme 5B). Based on the above results and relevant literature reports,[28] a plausible mechanism has been depicted in Scheme 5C. Initially, sulfonimine **2e** ($E_{1/2}$ = −1.22 V vs. SCE of **2e**)[19] undergoes single-electron reduction by the excited-state photocatalyst ($E_{1/2}$ (Ir(IV)/Ir(III)*) = −1.73 V vs. SCE),[29] forming the sulfonyl radical **I**. Subsequently, the radical **I** adds onto the strained C-C σ bond of BCB **1a** to give intermediate **II** that could undergo cyclization followed by single-electron oxidation and deprotonation to give the spirocyclic product **3a** while closing the photocatalytic cycle. To comprehend the diastereoselective outcome, we have carried out a DFT study at the $SMD_{(Acetonitrile)}$/UM06-2x/6-311++G(d,p)// $SMD_{(Acetonitrile)}$/UM06-2x/6-31G(d) level of theory. The radical spirocyclization step was found to proceed through two diastereomeric transition states, **TS-2a** and **TS-2b**, which differ in energy by only 0.8 kcal·$mol^{-1}$ (see SI for full details), and it is in good agreement with the observed diastereomeric ratio (Scheme 5D). However, when sulfonyl chloride was employed as a radical precursor, a competitive reaction pathway involving the abstraction of the chlorine atom was found via **TS-3**, giving **4b**, which explains the formation of direct addition product **4a** observed during our initial investigations (Fig. 1, column 1).

In conclusion, we have disclosed a new strain-release spirocyclization strategy to synthesize a library of functionalized spirocyclobutyl oxindoles. The use of sulfonimines is the key to the success of this reaction, as it suppresses the direct addition product. The reaction exhibits a broad scope towards the BCB amides and sulfonimines with excellent functional group tolerance. Notably, phosphonyl and trifluoromethyl radicals were added to the strained C-C σ bond to access phosphonylated and trifluoromethylated spirocyclobutyl oxindole derivatives. Additionally, the obtained products could be efficiently transformed into valuable building blocks. DFT studies were used to rationalize the observed reactivity and stereoselectivity. We anticipate that this strategy will expand the use of strain-release in synthesizing other spirocyclobutyl oxindoles due to the vast abundance and diversity of radical precursors.

ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://xxxxxxxxxxxx.

General experimental procedures, optimization of the reaction, mechanistic experiments, X-ray structure of **3a** and **3b**, characterization and crystal data, and NMR spectra of new compounds (PDF).

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### Author Contributions

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