OL Organic Letters

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

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Cite This: https://doi.org/10.1021/acs.orglett.4c02177 Read Online

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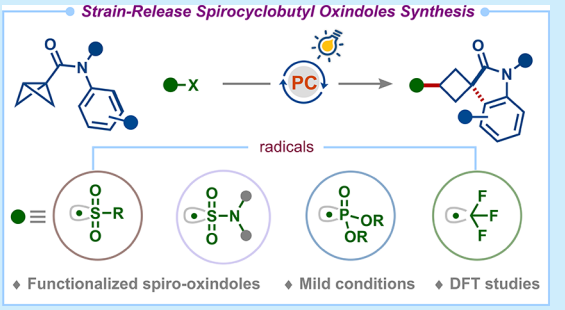
ABSTRACT: Spirocyclobutyl oxindoles have garnered substantial attention in drug discovery and pharmaceuticals owing to their wide range of biological activities. Strain-release in small-ring compounds is a powerful strategy to enable efficient access to complex molecules. In this study, we successfully 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.



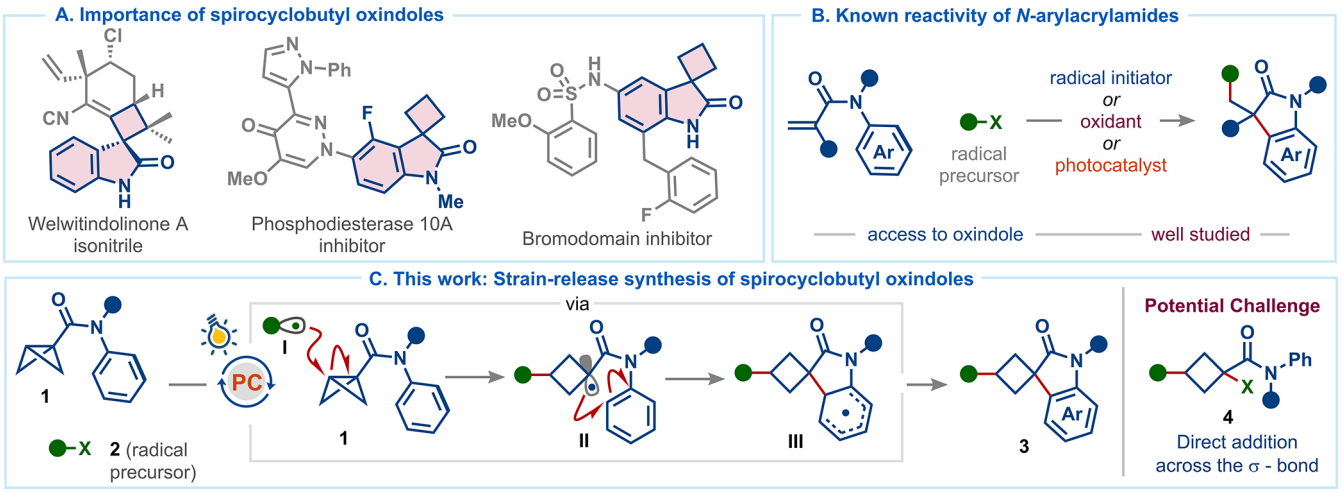
Spirocyclic scaffolds have been recognized as potential pharmacophores in drug discovery and pharmaceuticals because of their unique and inherently rigid three-dimensional architecture.[1] The conformational rigidity ensures that substituents are positioned in a well-defined and highly predictable manner and allows efficient interactions of ligands with binding sites.[2] Precisely controlling the 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.[1b] 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 activity,[4] action as phosphodiesterase inhibitors (for the treatment of Parkinson's disease),[5] and bromodomain inhibition (Scheme 1A). Despite these attractive features, there is a limited range of strategies available for the synthesis of spirocyclobutyl oxindoles.[6] Although these strategies are very effective, they either require stoichiometric oxidants[6b] or are limited to carbon-centered radicals.[6c] Consequently, modular, catalytic, and sustainable methods for accessing functionalized spirocyclobutyl oxindoles with diverse functional handles 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.[7] In particular, bicyclo[1.1.0]butane (BCB) derivatives have enormous synthetic potential and have attracted 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.[8] The strained C−C σ-bond of BCB derivatives was reported to participate in various cycloadditions,[9] difunctionalizations,[10] carbene insertions,[11] and cascade reactions[12] 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 in either electron transfer or energy transfer processes with organic molecules have evolved into efficient synthetic tools 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.

In analogy to the known reactivity of *N*-arylacrylamides (Scheme 1B),[13] 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 the radical intermediate **III**. Finally, single-electron oxidation of **III** by the oxidized photocatalyst followed by deprotonation

Received: June 13, 2024
Revised: July 19, 2024
Accepted: July 23, 2024

Scheme 1[a]



[a](A) Importance of spirocyclobutyl oxindoles. (B) Known reactivity of *N*-arylacrylamides to access oxindoles. (C) This work: strain-release-driven synthesis of spirocyclobutyl oxindoles.

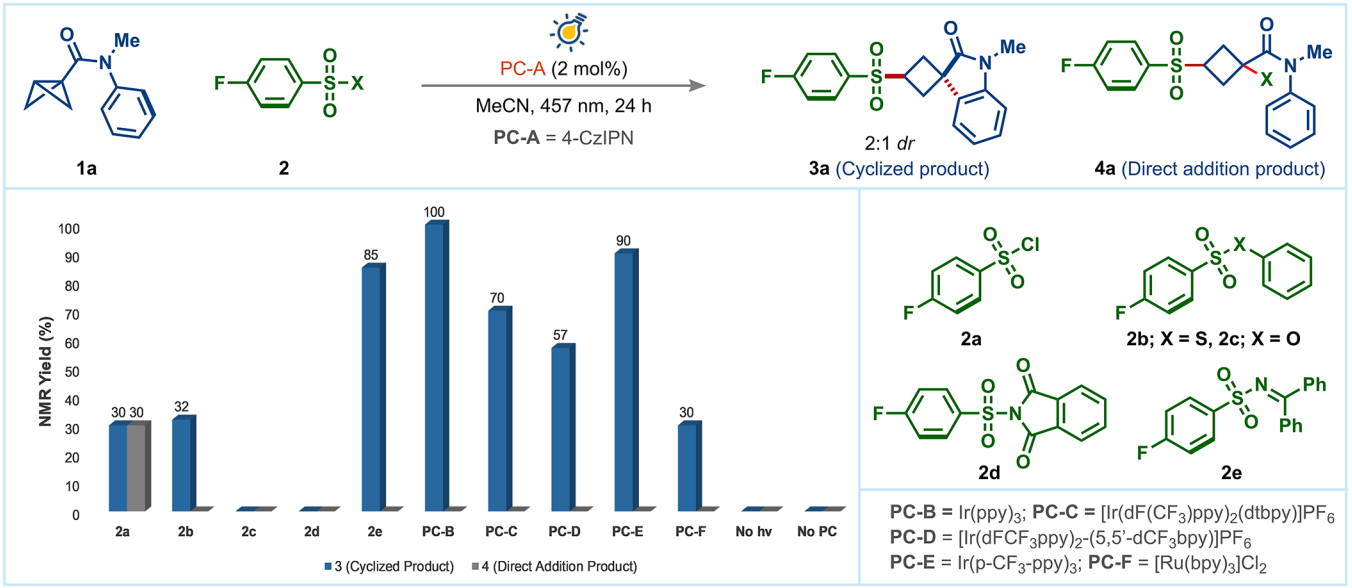


Figure 1. Optimization of the reaction conditions. General conditions: **1a** (0.1 mmol), **2** (1.0 equiv), MeCN (0.1 M), PC (2 mol %), 457 nm, 24 h. Light source: Photocube. 4-CzIPN was used as a photocatalyst in columns 1−5. dr for **3a** is 2:1. Yields and dr were determined from the crude reaction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

leads to the formation of spirocyclobutyl oxindole **3** while completing the photocatalytic cycle (Scheme 1C). However, we identified a major issue associated with this hypothesis: the radical intermediate **II** could undergo direct addition before cyclization to give the direct addition product **4**. Despite this challenge, here we report our success in developing a photoredox-catalyzed radical spirocyclization strategy for accessing functionalized spirocyclobutyl oxindoles (Scheme 1C). The formation of the direct addition product was prevented by selecting a suitable radical precursor. We have successfully added sulfonyl, phosphonyl, and trifluoromethyl radicals to BCB amides to access sulfonylated, phosphonylated, and trifluoromethylated spirocyclobutyl oxindoles. It is important to note that phosphonyl radicals have not been added to the strained C−C σ-bond of BCB to date. Furthermore, the obtained products could be transformed into valuable building blocks. A DFT study 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 as a 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 (Figure 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 nonhalogenic 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 (Figure 1, column 2). Phenyl 4-fluorobenzenesulfonate (**2c**)

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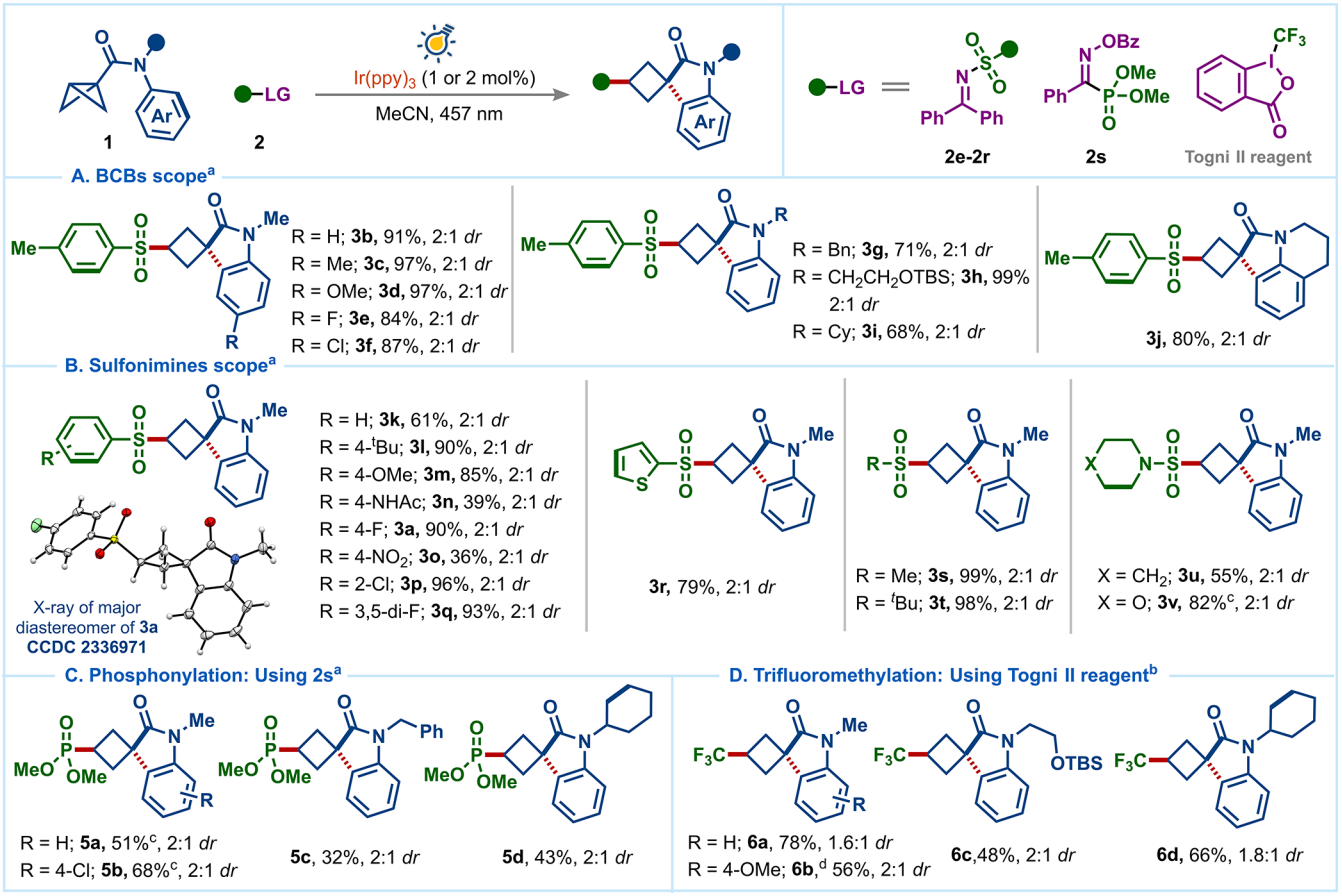
Scheme 2. Scope of the Reaction



[a]Reaction conditions: **1** (0.3 mmol), **2** (1.2 equiv), and $Ir(ppy)_3$ (2 mol %) in MeCN (0.1 M), 457 nm, 12−24 h. [b]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. Yields are of isolated products, and dr was determined by ^{1}H NMR from the crude reaction mixture. [c]0.2 mmol scale. [d]0.15 mmol scale.

and 2-((4-fluorophenyl)sulfonyl)isoindoline-1,3-dione (**2d**) did not provide the desired spirocyclobutyl oxindole product **3a** (Figure 1, columns 3 and 4). The lack of reactivity observed with **2c** could be due to its high reduction potential ($E_{1/2}$ = −2.03 V vs SCE),[14] whereas the lack of reactivity of the radical precursor **2d** can be attributed to its poor solubility in acetonitrile. Next, our focus shifted toward employing *N*-(diphenylmethylene)-4-fluorobenzenesulfonamide (**2e**), previously used by the groups of Glorius[15a] and Du[15b] for the 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 (Figure 1, column 5). The excellent reactivity of **2e** can be attributed to its low reduction potential ($E_{1/2}$ = −1.22 V vs SCE).[14] These promising results encouraged us to optimize the reaction conditions further by employing tunable metal-based photocatalysts. Among the photocatalysts screened (Figure 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 the photocatalyst and light irradiation were essential for reactivity (Figure 1, columns 11 and 12).

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 spirocyclobutyl oxindole **3b** in 91% yield. The reaction was amenable to scaling up, with product **3b** formed in a 74% yield on a 2.4 mmol scale. The structure of the minor diastereomer of **3b** was determined by X-ray analysis (CCDC 2336969). Various aryl rings in BCB amides bearing electron-donating and electron-withdrawing substituents were well tolerated, providing 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 products **3g**−**3i** in good yields. The tetrahydroquinoline-derived BCB gave the spirooxindole product **3j** in 80% yield. Subsequently, the scope and generality of 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, participated well in this reaction (products **3k**−**3m**). A sulfanilamide derivative could also be used as a sulfonyl radical precursor to access spirocyclobutyl oxindole **3n** in 39% yield. Electron-deficient aryl-sulfonimines were also viable substrates in this reaction, giving the products **3a** (CCDC 2336971) and **3o**. The *ortho*- and *meta*-substituted sulfonimines also yielded the products **3p** and **3q**, respectively, in excellent yields. A heterocyclic sulfonimine, such as 2-thiophenyl, was also found to be a suitable substrate in this reaction (product **3r**). Additionally, sulfone radicals bearing alkyl substituents were tolerated and furnished the corresponding spirocyclobutyl oxindoles **3s** and **3t** in high yields.

https://doi.org/10.1021/acs.orglett.4c02177
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Pleasingly, the synthesis of **3s** was scaled up to 6 mmol, providing 1.12 g of the product in 70% yield. 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 products **3u** and **3v**, respectively, in good yields.

Phosphorus-embedded scaffolds are present in several bioactive molecules and pharmaceuticals owing to their ability to regulate a wide range of cellular processes, including protein signaling,[16] gene expression,[17] and cellular metabolism.[18] Considering the multifunctional role of these scaffolds, we were interested in incorporating the phosphonate moiety into spirocyclobutyl oxindole. For this reason, we employed the radical precursor **2s**[19] in our strain-release method to enable the synthesis of C(sp^3)−P(V) cyclobutane-containing spirooxindoles. When we subjected phosphonyl radical precursor **2s** to our standard conditions, we obtained desired products **5a**−**5d** in moderate to good yields (Scheme 2C). To the best of our knowledge, there are no reports on the addition of phosphonyl radicals to the bicyclobutane system.

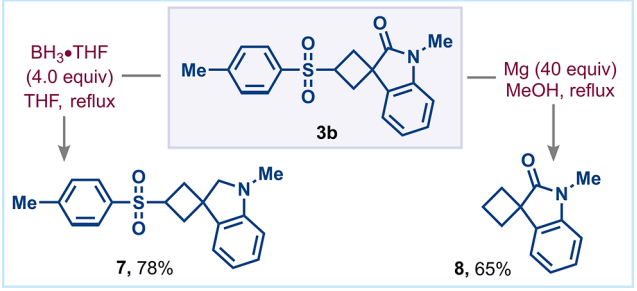
Incorporating fluorinated functionalities, particularly the trifluoromethyl motif, into a therapeutic or diagnostic small molecule can enhance its pharmacokinetics and physicochemical properties.[20] Thus, introducing the trifluoromethyl group onto spirocyclobutyl oxindoles could enhance their biological 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 **6a** was obtained with a moderate yield. A quick optimization (see 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 2D).

The obtained product **3b** could be efficiently converted to the spirocyclobutyl dihydroindole derivative **7**, another important motif in medicinal chemistry,[21] in 78% yield by treatment with borane. The sulfone group could be easily removed under reflux conditions using Mg in methanol to afford product **8** in 65% yield (Scheme 3).

We next turned our attention to the mechanism of the reaction. Based on the radical trapping experiments, luminescence quenching experiments, and cyclic voltammetry, a plausible mechanism has been depicted (Figure 6 in the SI). Initially, sulfonimine **2e** ($E_{1/2}$ = −1.22 V vs SCE of **2e**)[14] undergoes single-electron reduction by the excited-state photocatalyst ($E_{1/2}$(Ir(IV)/Ir(III)*) = −1.73 V vs SCE),[22] forming the sulfonyl radical **I**. Subsequently, radical **I** adds onto the strained C−C σ-bond of BCB **1a** to give the more stable tertiary radical **II** that can undergo cyclization, followed by single-electron oxidation and deprotonation to give spirocyclic product **3a**. To comprehend the diastereoselective outcome, we have carried out a DFT study at the SMD$_{(MeCN)}$/UM06−2x/6-311++G(d,p)//SMD$_{(MeCN)}$/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}, in good agreement with the observed diastereomeric ratio (Scheme 4). 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 (Figure 1, column 1).

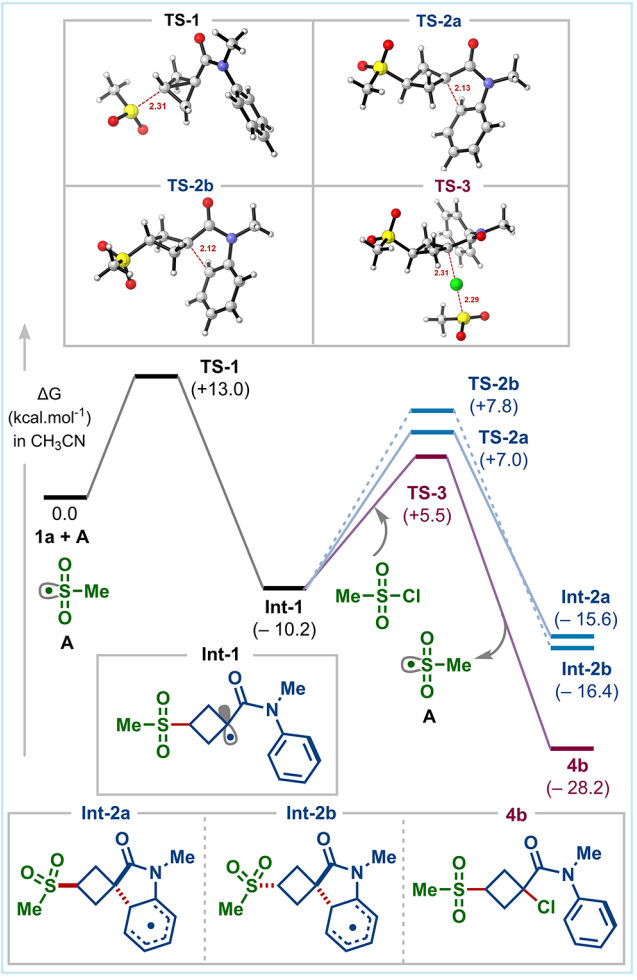
In conclusion, we have disclosed a new strain-release spirocyclization strategy to synthesize a library of functionalized spirocyclobutyl oxindoles.[23] The use of sulfonimines is the key to the success of this reaction, as they suppress the direct addition product. The reaction exhibits a broad scope toward 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

Scheme 3. Synthetic Utility[a]



[a]Reactions were performed in a 0.1 mmol scale.

Scheme 4. DFT Study: Energy Profile Diagram



https://doi.org/10.1021/acs.orglett.4c02177
Org. Lett. XXXX, XXX, XXX−XXX

access phosphonylated and trifluoromethylated spirocyclobutyl oxindole derivatives. Additionally, the obtained products could be efficiently transformed to 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 oxindole derivatives due to the vast abundance and diversity of radical precursors.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.4c02177.

General information, experimental procedures, characterization data, NMR spectra for all new compounds, and DFT study data (PDF)

Accession Codes

CCDC 2336969 and 2336971 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support from the SERB, Govt. of India (File CRG/2022/007372), is greatly acknowledged. D.P.H. thanks IISc Bangalore for the infrastructure. T.S. thanks the Ministry of Education, Govt. of India, for PMRF. N.A.B. thanks KVPY for the fellowship. We thank Prof. Garima Jindal (IISc Bangalore) for helpful discussions on the DFT model.

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https://doi.org/10.1021/acs.orglett.4c02177
Org. Lett. XXXX, XXX, XXX−XXX