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Visible-Light-Mediated Strain-Release Radical Spirocyclizations: Access to Functionalized Spirocyclobutanes

Tushar Singha, Durga Prasad P Hari.

Affiliations below.

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Abstract:
Spirocyclobutanes have gained significant attention in medicinal chemistry discovery programs due to their broad spectrum of biological activities and clinical applications. Utilizing ring strain in small molecules to drive organic transformations is one of the most powerful tools in chemical synthesis. Our research group has focused on developing new synthetic strategies enabled by ring-strain to construct complex molecules selectively and efficiently. This account summarizes our recent efforts toward the synthesis of a library of functionalized spirocyclobutanes by harnessing ring-strain of bicyclo[1.1.0]butanes (BCBs). Three different spicrocyclization cascades have been developed to incorporate a diverse range of radical precursors into spirocycobutanes.

Corresponding Author:
Dr. Durga Prasad P Hari, Indian Institute of Science, Organic Chemistry, New Chemical Science Building, 560012 Bangalore, India, dphari@iisc.ac.in

Affiliations:
Tushar Singha, Indian Institute of Science, Organic Chemistry, Bangalore, India
Durga Prasad P Hari, Indian Institute of Science, Organic Chemistry, Bangalore, India

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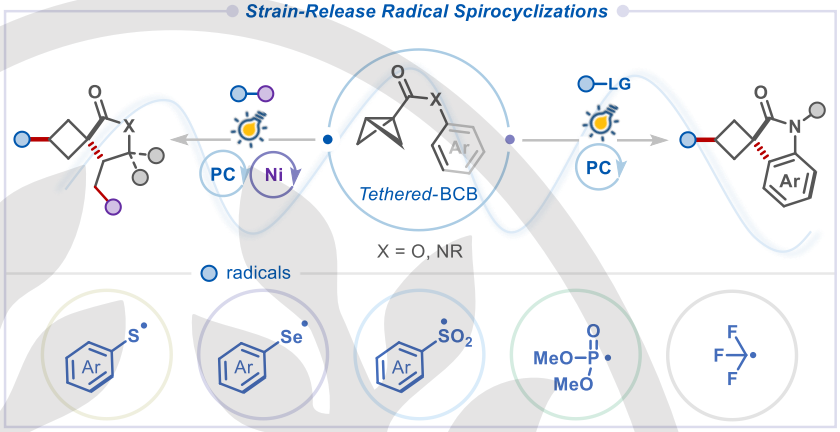
Tushar Singha
Durga Prasad Hari*

Department of Organic Chemistry, Indian Institute of Science, Bangalore, India, 560012.

dphari@iisc.ac.in



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Abstract Spirocyclobutanes have gained significant attention in medicinal chemistry discovery programs due to their broad spectrum of biological activities and clinical applications. Utilizing ring strain in small molecules to drive organic transformations is one of the most powerful tools in chemical synthesis. Our research group has focused on developing new synthetic strategies enabled by ring-strain to construct complex molecules selectively and efficiently. This account summarizes our recent efforts toward the synthesis of a library of functionalized spirocyclobutanes by harnessing ring-strain of bicyclo[1.1.0]butanes (BCBs). Three different spicrocyclization cascades have been developed to incorporate a diverse range of radical precursors into spirocycobutanes.

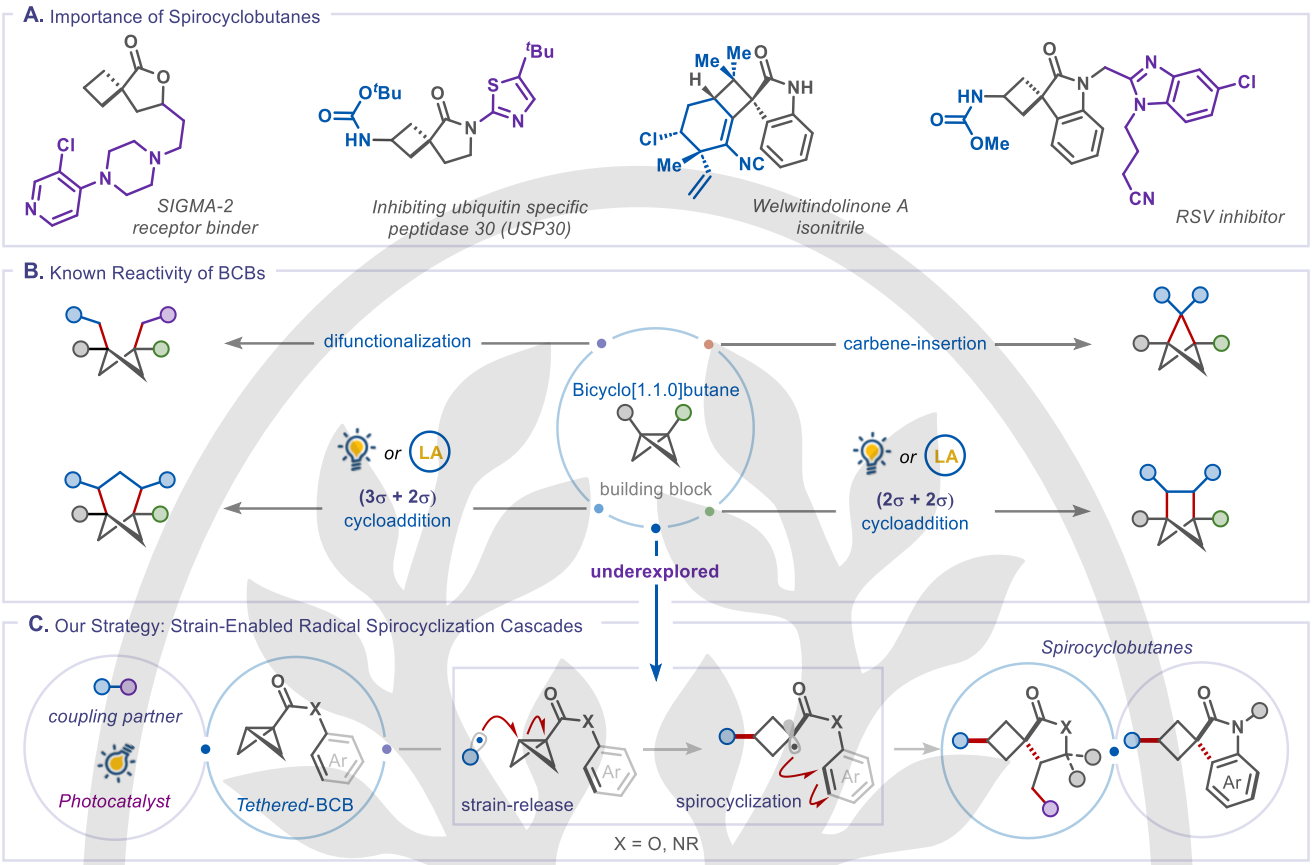
1. Introduction
2. Synthesis of Spirocyclobutyl Lactones and -Lactams using Bifunctional Reagents
3. Dual Photoredox/Nickel Catalysis for the Synthesis of Spirocyclobutyl Lactams
4. Synthesis of Spirocyclobutyl Oxindoles under Photoredox Catalysis
5. DFT Studies
6. Conclusion

Key words: Bicyclo[1.1.0]butane, Strain-release, Photoredox catalysis, Radicals, Spirocyclobutanes, Dual catalysis, Bifunctional reagents

1. Introduction

Under the concept of "escape from flatland," spirocyclic compounds have become important in developing small-molecule drug candidates owing to their unique three-dimensional (3D) architecture.[1] The rigidity of the spirocyclic motif allows for the precise control of the spatial arrangement of substituents, which is particularly beneficial for designing ligands that can interact effectively with 3D sites.[2] This structural rigidity enhances the specificity and potency of the interactions and thus improves pharmacokinetic and physicochemical properties. As a result, spirocyclic compounds are becoming increasingly prominent structural motifs in medicinal chemistry discovery programs.[3] Among the various spirocyclic compounds, spirocyclobutanes are particularly fascinating due to their high rigidity, resulting in well-defined exit vectors. Incorporating a cyclobutane ring into spirocyclic compounds contributes to conformational rigidity and improves metabolic stability, lipophilicity, and acidity/basicity compared to other cyclic structures.[4] These salient factors make spirocyclobutanes valuable scaffolds for drug development.[5] Spirocyclobutane derivatives, including spirocyclobutyl lactones, -lactams, and -oxindoles, have been recognized for their potential as pharmacophores due to their desirable physicochemical properties and a wide range of biological applications, making them highly valuable in the search for new therapeutic agents (Scheme 1A).[4,6] Consequently, there is a surge in the exploration of these motifs in medicinal chemistry.[7]

The ring-strain energy of organic molecules is a powerful propelling force that facilitates unique reactivity, primarily by relieving ring-strain. This phenomenon drives a wide range of valuable synthetic transformations with numerous applications across multiple research domains, such as total synthesis, bioisosterism, bioconjugation, and polymer science.[8] Among strained organic small molecules, bicyclo[1.1.0]butane (BCB) is the smallest fused strained hydrocarbon possessing a ~64 kcal/mol strain energy. It has garnered substantial attention over recent years among synthetic and medicinal chemists due to its ability to unlock challenging strategies for accessing valuable scaffolds that are otherwise difficult to access.[9] The strained C–C σ bond of BCB derivatives is known for its involvement in numerous transformations. For example, difunctionalization,[10] cycloaddition,[11] ene-type,[12] and carbene insertions[13] under a Lewis-acid catalyzed or photochemical conditions, leading to 1,3-disubstituted cyclobutanes, bicyclic carbocycles, and heterocycles, which are bioisosteres of (hetero)arenes (Scheme 1B).



Scheme 1: (A) Representative examples of bioactive compounds containing spirocyclobutanes. (B) Diverse known reactivity of BCBs. (C) Strain-enabled radical spirocyclization cascades

In this account, we discuss various strain-enabled radical spirocyclization strategies developed by our research group (Scheme 1C). These strategies allow the introduction of different functional groups such as thiyl, selenyl, sulfonyl, phosphonyl, and trifluoromethyl, providing rapid access to a new library of spirocyclobutyl lactones, -lactams, and -oxindoles.

Tushar Singha earned his B.Sc. in Chemistry from the University of Kalyani in 2018 and his M.Sc. from IIT Madras in 2020. During his M.Sc., he worked on copper-catalyzed C-S bond formation with Prof. G. Sekar. He is currently pursuing Ph.D. at the Indian Institute of Science, Bangalore with Dr. Durga Prasad Hari. His research interests are focused on ring-strain release and photo- and electrochemical strategies in organic synthesis.

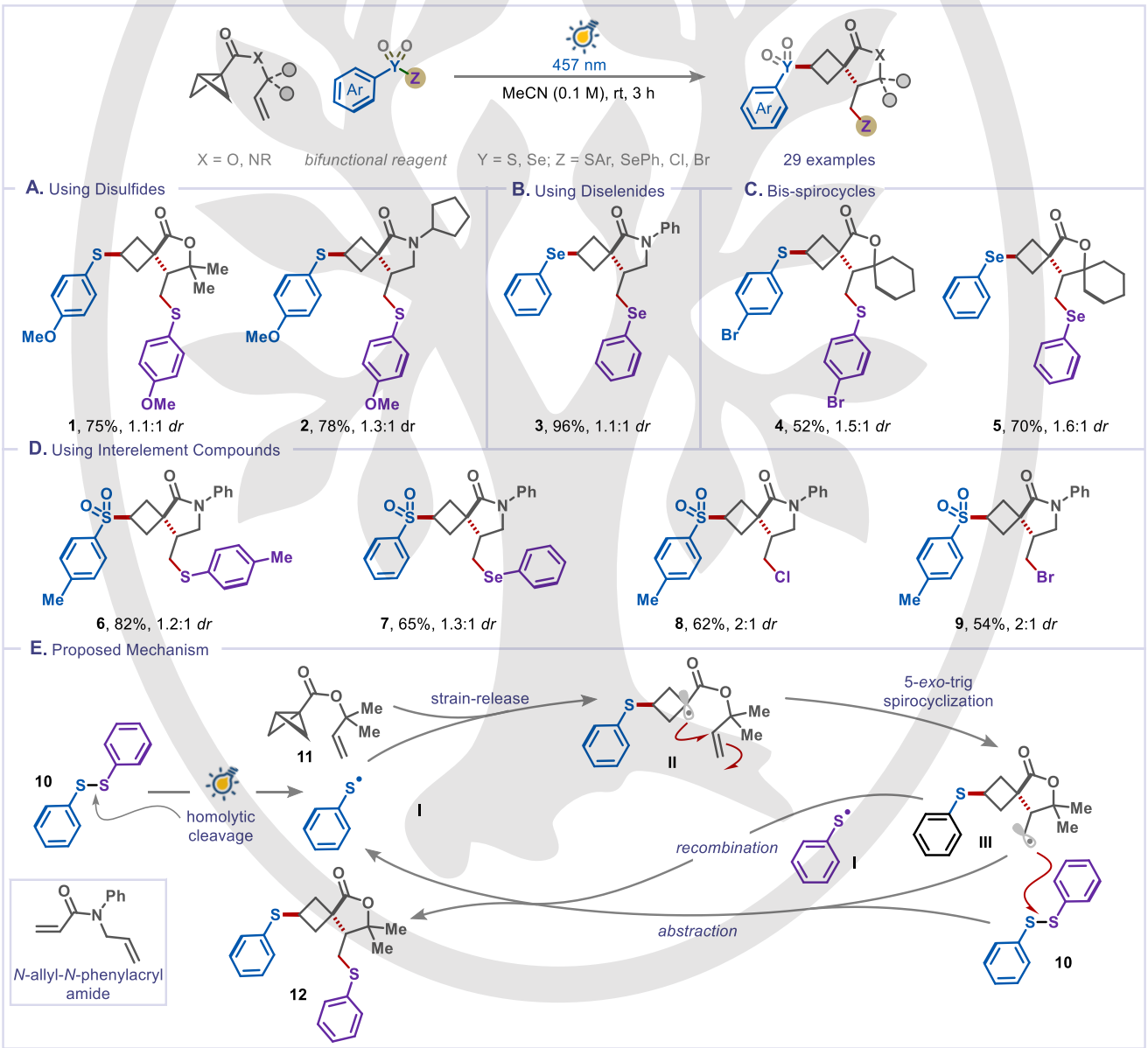
Durga Prasad Hari received his MSc degree from IIT Madras in 2010. He then moved to the University of Regensburg, Germany, where he pursued his Ph.D. with Prof. Burkhard Koenig. In 2014, following his graduate education, he was a postdoctoral fellow in the laboratory of Prof. Jerome Waser at EPFL, Switzerland. In 2018, he joined the Aggarwal group at the University of Bristol as a Marie-Curie research fellow. Since March 2021, he has been holding an assistant professor position at the Indian Institute of Science, Bangalore. His research interests focus on discovering new reactivity in organic synthesis by harnessing the high reactivity of strain-embedded molecules and carbenes through photo- and electrochemical strategies.

2. Synthesis of Spirocyclobutyl Lactones and -Lactams using Bifunctional Reagents

Achieving sustainability and selectivity in chemical synthesis is one of the primary goals of modern organic and medicinal chemistry. Bifunctional reagents minimize waste generation while providing an atom-economical approach to chemical complexity, either as dual coupling partners or in combination with an activating species as a coupling partner.[14] Diaryl disulfides and diaryl diselenides are well-known bifunctional reagents that are reported to be added across unsaturated bonds and strained C-C σ bonds under heating/photochemical conditions to provide functionalized products.[15]

Very recently, using tethered BCBs and diaryl disulfide as bifunctional reagents under visible-light irradiation, our research group successfully achieved a radical spirocyclization cascade.[16] The methodology exhibits a remarkable substrate scope and excellent functional group compatibility. Spirocyclobutyl lactone and -lactams (**1** and **2**) were obtained in excellent yields with high chemoselectivity (Scheme 2A). Organoselenium compounds are found in various bioactive molecules and serve as highly valuable synthetic intermediates. Diphenyl diselenide successfully underwent the desired spirocyclization reaction, affording spirocycle **3** (Scheme 2B). Notably, bis-spirocycle **4** and **5** could also be accessed using diphenyl disulfide and diphenyl diselenide, respectively (Scheme 2C). Various interelement reagents also successfully engaged in this transformation, affording the desired spirocyclic products **6-9** with excellent chemoselectivity (Scheme 2D).

A plausible mechanism has been proposed based on control experiments and relevant literature reports (Scheme 2E). First, irradiation with visible light leads to the homolytic cleavage of PhSSPh **10** and furnishes a thiyl radical **I**. Subsequent addition of radical **I** to the strained C-C σ-bond of BCB **11** generates a *tertiary* radical intermediate **II**. Next, radical **II** undergoes 5-*exo*-trig spirocyclization to give a primary radical intermediate **III**. Finally, radical **III** abstracts an SPh group from another PhSSPh molecule and furnishes product **12**. Nonetheless, the possibility of radical **III** recombining with thiyl radical **I** to form the product cannot be excluded. The unreactivity with *N*-allyl-*N*-phenylacrylamide under optimized reaction conditions highlighted the essential role of ring strain in driving the spirocyclization cascade (Scheme 2E).



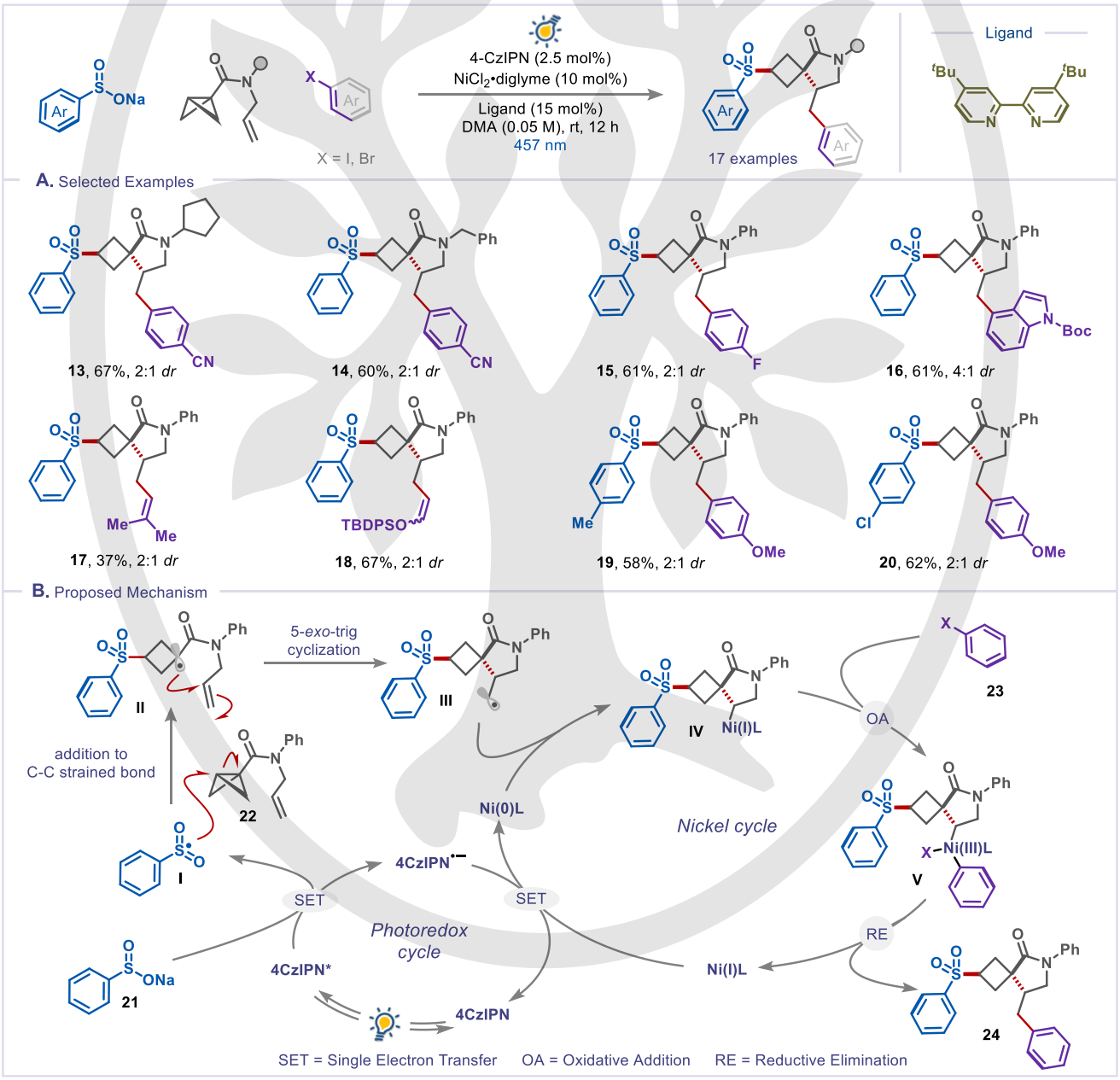
Scheme 2: Scope of spirocyclobutyl lactones and -lactams using bifunctional reagents. (A) Scope using diaryl disulfides. (B) Scope using diaryl diselenides. (C) Bis-spirocycles. (D) Scope using various interelement compounds. (E) Plausible reaction mechanism.

3. Dual Photoredox/Nickel Catalysis for the Synthesis of Spirocyclobutyl Lactams

Dual nickel/photoredox catalysis has established itself as a promising synthetic strategy for enabling alkyl radical cross-coupling reactions with diverse electrophiles. In these transformations, alkyl radicals are generally produced either through direct homolysis of C(sp^3)–X bonds or via indirect pathways, including cyclization, β-scission, or 1,5-HAT, yielding new radicals that engage in the subsequent nickel-catalyzed cross-coupling reaction.[17] We successfully realized a novel dual nickel/photoredox catalyzed three-component cross-coupling of BCB allyl amides with aryl sulfinates and (hetero)aryl halides. This protocol allows for the modular synthesis of a broad range of complex spirocyclic scaffolds by leveraging easily accessible aryl sulfinates and (hetero)aryl or alkenyl halides (Scheme 3).[16] This is the only example so far reported in the literature on the cross-coupling of alkyl radicals generated through a strain-enabled radical cascade.

The reaction showed a broad substrate scope and excellent functional group tolerance (Scheme 3A). Various groups attached to the nitrogen atom of BCB allyl amides, such as cyclopentyl, benzyl, and phenyl, were well tolerated (products **13**-**15**). A broad range of (hetero)aryl and alkenyl halides were also successfully coupled in this transformation (products **15**-**18**). Aryl sulfinates bearing electron-donating and electron-withdrawing substituents were also viable substrates, affording corresponding spirocycles **19** and **20**.

The mechanism for this dual-catalyzed conjunctive cross-coupling begins with single electron transfer (SET) by phenyl sulfinate **21** to excited state photocatalyst, generating a sulfonyl radical **I** (Scheme 3B). Adding the sulfonyl radical **I** onto the

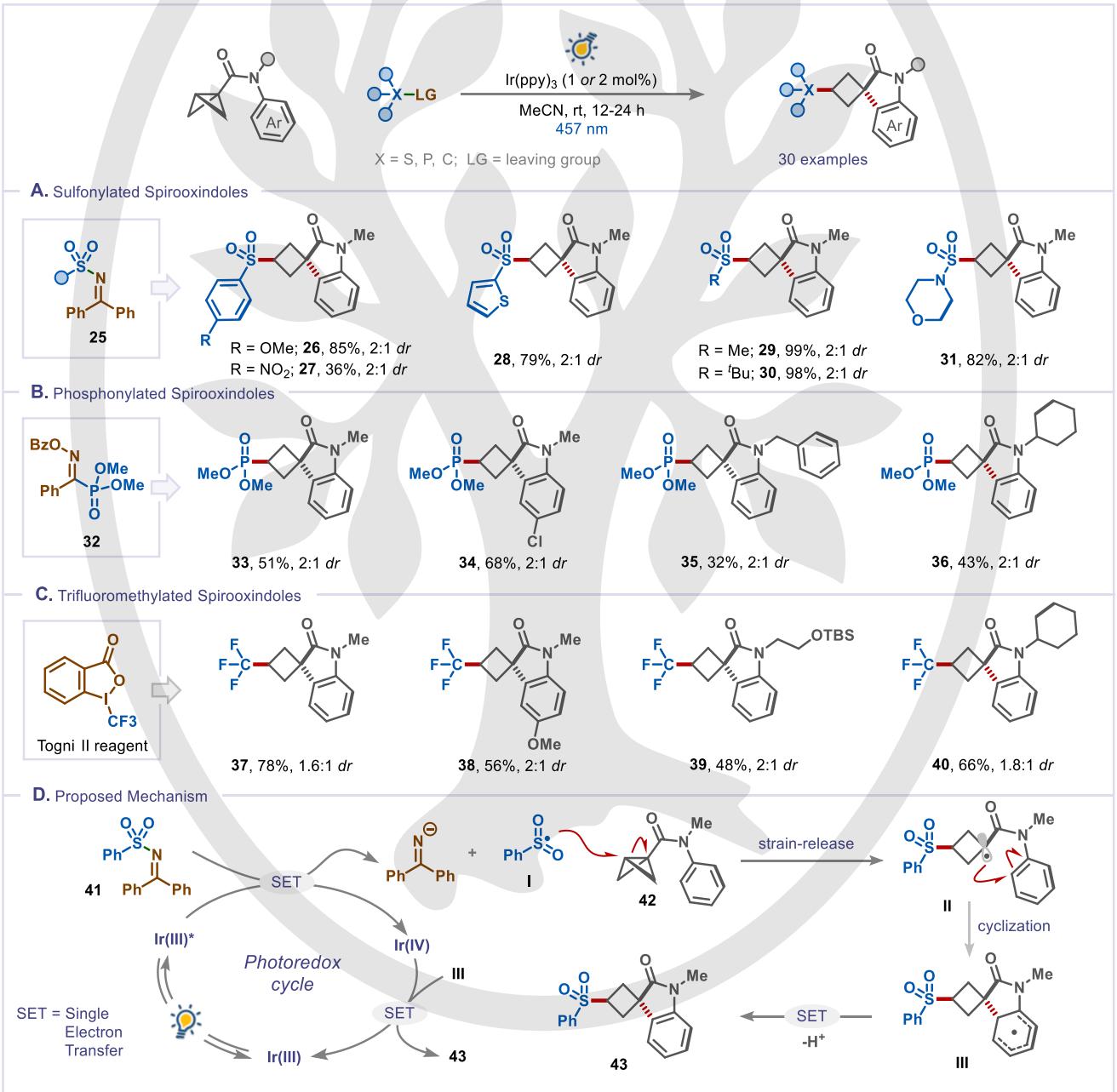


Scheme 3: Synthesis of spirocyclobutyl lactams using dual photoredox/nickel catlysis. (A) Representative examples of the scope. (B) Proposed reaction mechanism.

strained C-C σbond of BCB **22** gives a *tertiary* radical **II** that undergoes 5-*exo*-trig spirocyclization to furnish a primary alkyl radical **III**. Subsequently, radical **III** is captured by Ni(0) species and furnishes the Ni(I) species **IV**. The iodobenzene **23** adds oxidatively to the Ni(I) species, following reductive elimination, affords the spirocyclic product **24** and Ni(I) species. Finally, single electron reduction of the Ni(I) species to Ni(0) by the reduced photocatalyst completes both catalytic cycles.

4. Synthesis of Spirocyclobutyl Oxindoles under Photoredox Catalysis

Despite having a broad array of biological applications (Scheme 1A), the strategies available for synthesizing spiro cyclobutyl oxindoles remain limited. In this regard, the development of modular, catalytic, and sustainable methods for synthesizing functionalized spirocyclobutyl oxindoles with diverse functional groups is highly desirable and could significantly contribute to the discovery of novel bioactive compounds. We have recently developed a photocatalyzed redox-neutral spirocyclization cascade to synthesize spirocyclobutyl oxindoles (Scheme 4).[18] Various radicals, including sulfonyl, phosphonyl, and trifluoromethyl were added successfully to BCB amides to obtain sulfonylated, phosphonylated, and trifluoromethylated spirocyclobutyl oxindoles. Aryl, heteroaryl, alkyl, and morpholine-substituted *N*-sulfonyl imine radical precursors (**25**) participated well in this reaction, successfully yielding the desired spirocycles **26-31** in excellent yields (Scheme 4A).



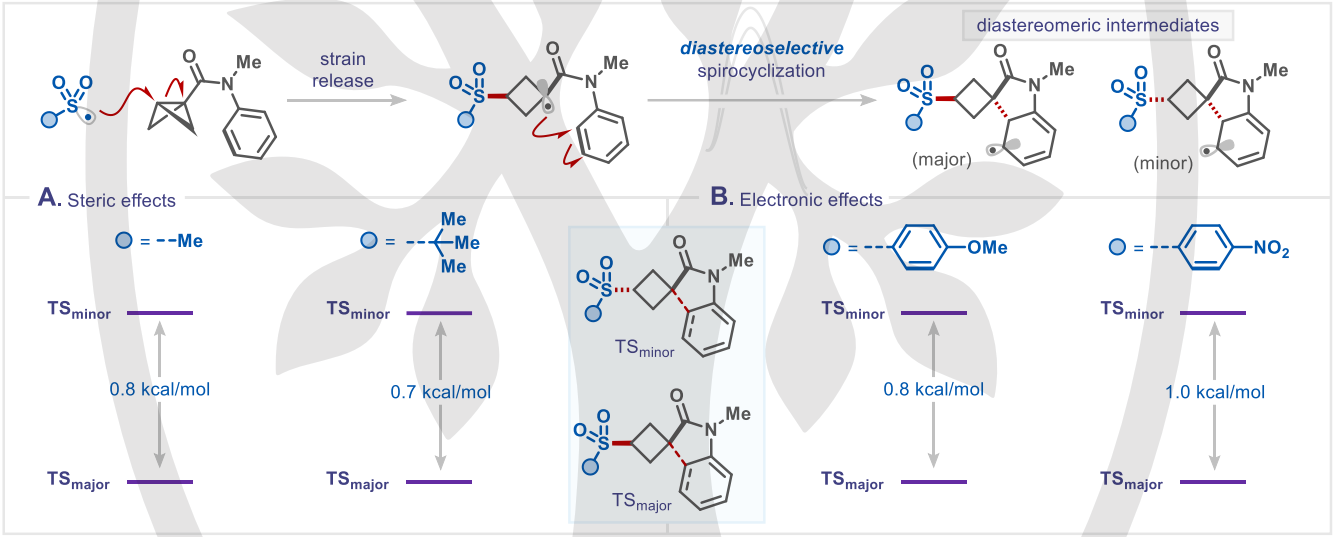
Scheme 4: Synthesis of spirocyclobutyl oxindoles. (A) Sulfonylated spirocyclobutyl oxindoles. (B) Phosphonylated spirocyclobutyl oxindoles. (C) Trifluoromethylated spirocyclobutyl oxindoles. (D) Proposed mechanism.

Phosphorus-containing structural motifs are found in numerous bioactive substances and pharmaceutical products due to their capability to regulate various cellular processes, such as protein signaling and gene expression.[19] Given the multifunctional role of these scaffolds, the phosphonyl radical precursor **32** was employed in this strategy to synthesize C(sp^3)–P(V) containing spirocyclobutane-oxindole products **33-36** in good yields (Scheme 4B). Incorporating fluorinated groups into therapeutic or diagnostic small molecules augments their biological activities.[20] Thus, adding a trifluoromethyl group to spirocyclobutyl oxindoles could potentially improve their biological activity. Using the Togni II reagent, aryl- and nitrogen-substituted BCBs effectively provided the trifluoromethylated spirocyclobutyl oxindoles **37-40** with moderate to good yields (Scheme 4C).

The reaction mechanism begins with oxidative quenching of the excited-state photocatalyst by sulfonimine **41**, generating sulfonyl radical **I**. Radical **I** then reacts with the strained C–C σ bond of BCB **42** to produce the radical intermediate **II**. A subsequent dearomative cyclization forms radical **III**. Finally, single-electron oxidation of radical **III** by the oxidized photocatalyst, followed by proton elimination, affords the desired product **43** and completes the photocatalytic cycles.

5. DFT Studies

To understand the diastereoselective outcome, a DFT study was conducted using the SMD(MeCN)/UM06-2x/6-311++G(d,p)//SMD(MeCN)/UM06-2x/6-31G(d) level of theory. Our DFT analysis revealed that the radical spirocyclization step proceeds via two diastereomeric transition states.[17] When methylsulfone radical is used, the diastereomeric transition states differ in energy by approximately 0.8 kcal/mol, which aligns well with the observed 2:1 diastereomeric ratio (Scheme 5A). To investigate the impact of a sterically hindered sulfone radical on the diastereomeric outcome, the *tert*-butyl sulfone radical was used. The energy difference between the diastereomeric states was found to be around 0.7 kcal/mol, which is consistent with the observed diastereomeric ratio. The observed poor diastereoselectivity is attributed to the lack of steric repulsion between SO_2R and the newly constructed spirocenter, which are two carbons away from each other, thus resulting in a low energy difference between the diastereomeric states. Finally, the electronic effects of the sulfone radical were examined using *p*-OMe and *p*-NO_2 substituted benzene sulfone radicals, and the results remained consistent (Scheme 5B). Thus, neither the steric nor the electronic effects of the sulfone radical significantly influence the diastereomeric outcome.



Scheme 5: DFT study: relative energies of the diastereomeric transition states. A) Steric effect on diasteroselectivity. B) Electronic effect on diasteroselectivity.

6. Conclusion

This account summarizes the strain-release spirocyclization strategies that significantly expand the toolkit for synthesizing functionalized spirocyclobutyl lactones, lactams, and oxindoles. By leveraging the inherent ring strain in BCB derivatives, we achieved high chemoselectivity and broad substrate scope under both catalyst-free and dual photoredox/nickel-catalyzed conditions. The successful incorporation of a range of functional groups, such as thiyl, selenyl, sulfonyl, phosphonyl, and trifluoromethyl groups, into spirocyclobutanes further underscores our approach's versatility and synthetic utility. We believe that the radical spirocyclization cascades discussed in this account will lay a solid foundation for further advancement in ring-strain chemistry and spirocycle synthesis due to the availability of a wide range of radical precursors and coupling partners.

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Conflict of Interest

There are no conflicts to declare

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