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ARTICLE

Electrochemically Driven Strain-Release Dearomative (3+2) Cyclization for the Synthesis of Bicyclo[2.1.1]hexane-Fused Polycyclic Spiroindolines

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Spiroindolines are ubiquitous structural motifs in natural products and biologically active compounds, making the development of reliable synthetic methods for their construction highly important to the synthetic chemistry community. Moreover, the synthesis of polycyclic compounds featuring C(sp³)-rich and complex three-dimensional (3D) architectures and multiple contiguous quaternary carbon centers in a single step remains a formidable challenge. Herein, we report an efficient and environmentally friendly electrochemical strategy for a dearomative (3+2) cyclization reaction of C3-bicyclo[1.1.0]butane (BCB)-substituted indoles. This method enables the efficient assembly of structurally complex and novel bicyclo[2.1.1]hexane (BCH)-fused polycyclic spiroindolines in high yields, featuring four contiguous stereogenic centers, two of which are spirocyclic all-carbon quaternary carbon centers. This new methodology provides a series of valuable spiroindolines under mild reaction conditions in a practical and atom-economic manner without the need for external oxidants, and the products can be further transformed into more complex spiroindolines. Notably, these C(sp³)-rich products exhibit significant potential in the field of medicinal chemistry.

Introduction

Dearomatization represents a powerful strategy for the efficient construction of sp³-rich, three-dimensional, and structurally complex polycyclic architectures from readily accessible aromatic feedstocks.¹⁻⁴ Owing to the broad spectrum of biological activities associated with indole derivatives,^{5, 6} the development of indole dearomatization reactions has emerged as an area of significant interest in synthetic chemistry.⁷ In particular, spiroindoline derivatives are privileged and valuable scaffolds that are prevalent in a great number of natural products and biologically active molecules, such as (+)-alstonlarsine A,^{8, 9} ajmaline,¹⁰ (+)-koumine^{11, 12} and anticancer agent (Scheme 1a).¹³ In drug structure optimization, the introduction of spirocycles and cyclobutane moieties significantly enhances the three-dimensional character of molecules and restricts bond stretching and rotation within molecular conformations, thereby stabilizing the presentation of a single pharmacophore conformation upon target binding, mediating desired pharmacological effects, and substantially reducing off-target effects and toxic side effects.¹⁴⁻¹⁹ Over the past decade, remarkable progress has been made in indole dearomative spiroannulation, driven primarily by transition-metal catalysis and visible-light catalysis,^{7, 20,}

²¹ thereby enabling the efficient construction of spiroindolines and spiroindolenines. Notably, Tang and co-workers reported the preparation of a class of tetracyclic cyclopenta-fused spiroindoline skeletons through Cu(II)-catalyzed intramolecular (3+2) annulation reactions of donor-acceptor cyclopropanes with indoles.²² However, the single-step synthesis of polycyclic spiroindolines with C(sp³)-rich complex three-dimensional (3D) structures and multiple contiguous quaternary carbon centers represents the most rapid and efficient approach, yet it remains a formidable challenge.

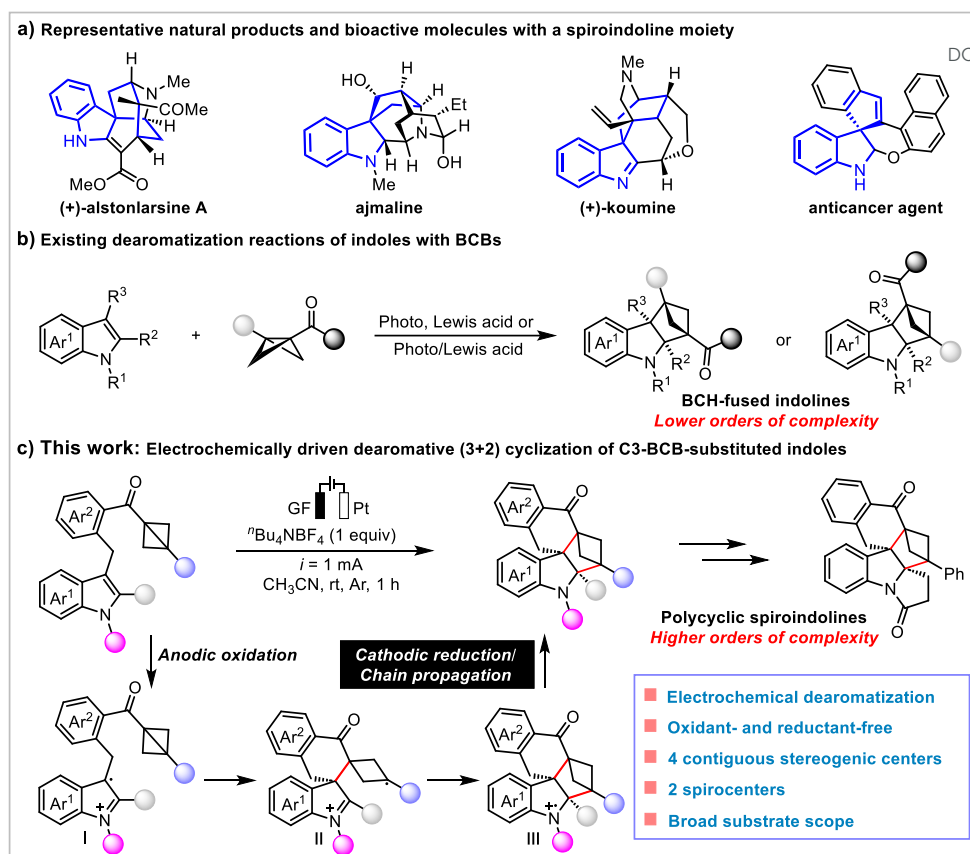
In recent years, bicyclo[1.1.0]butanes (BCBs) have gained widespread recognition as useful synthetic tools in (3+n) cycloaddition reactions,²³⁻³⁸ enabling the formation of C(sp³)-rich bicyclic hydrocarbons that serve as bioisosteres of aromatic rings in medicinal chemistry, due to their improved pharmacokinetic and physicochemical properties.³⁹⁻⁴² Benefiting from their distinctive ring strain and unique σ -bond framework, numerous BCB-based cycloaddition reactions have been developed, demonstrating exceptional reactivity and broad application potential in both polar and radical reaction systems. Among them, BCBs have been employed in the dearomatization cyclization reactions of indoles to access BCH-fused indolines. In 2022, Glorius et al. reported a representative photochemical [2 π +2 σ] cycloaddition between indoles and monosubstituted BCBs, leading to the formation of BCHs with a limited substrate scope.⁴³ In 2023, Deng and co-workers developed a Yb(OTf)₃ catalyzed intermolecular atom-economical cycloaddition of indoles with BCBs to provide a direct construction of polycyclic indoline skeletons.⁴⁴ In the same year, Feng et al. developed a silver-catalyzed dearomative [2 π +2 σ] cycloaddition

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Scheme 1. Overview of the work. a) Representative natural products and bioactive molecules with a spiroindoline moiety. b) Existing dearomatization reactions of indoles with BCBs. c) This work: Electrochemically driven dearomative (3+2) cyclization of C3-BCB-substituted indoles.

of *N*-unprotected 2-substituted indoles and bicyclobutanes for the synthesis of indoline fused BCHs with opposite regioselectivity compared to the classical pathway.⁴⁵ Very recently, Dong and coworkers investigated photocycloadditions of indole derivatives with monosubstituted BCBs by photoinduced chiral *N,N'*-dioxide/metal complex Lewis acid catalysis (Scheme 1b).⁴⁶ Despite these achievements, the synthesis of polycyclic spiroindolines with more intricate 3D configurations remains an exceptionally intriguing and highly valuable frontier for researchers, and the development of environmentally friendly and sustainable methodologies to construct such structures holds significant importance for both synthetic and medicinal chemistry.

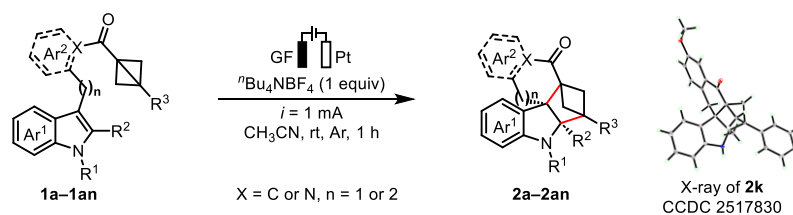
Electrochemistry, as a powerful and environmentally friendly platform for synthetic organic chemistry, is gaining increasing attention due to its inherent scalability, the ability to avoid harmful chemical oxidants and reductants, and the high tunability of reaction parameters.^{47–57} Furthermore, this strategy has also been successfully employed in dearomatization of indole to provide three-dimensional indolines of high-added value by Lei,^{58–61} Ling,⁶² Zhao,⁶³ Guo,⁶⁵ et al.^{66–70} Nonetheless, reports on the application of BCB in electrochemical systems remain very limited.^{37, 71, 72} To the best of our knowledge, the methods for obtaining polycyclic spiroindolines with two or more spirocenters through indole-based dearomatization reactions have not been reported. Moreover, to date, there have been no studies on the use of BCB in electrocatalytic indole dearomatization reactions for the construction of polycyclic spiroindole derivatives. Based on previous literature and our research on indole dearomatization reactions,⁷³ we speculate that

Table 1 Optimization of Reaction Conditions^a

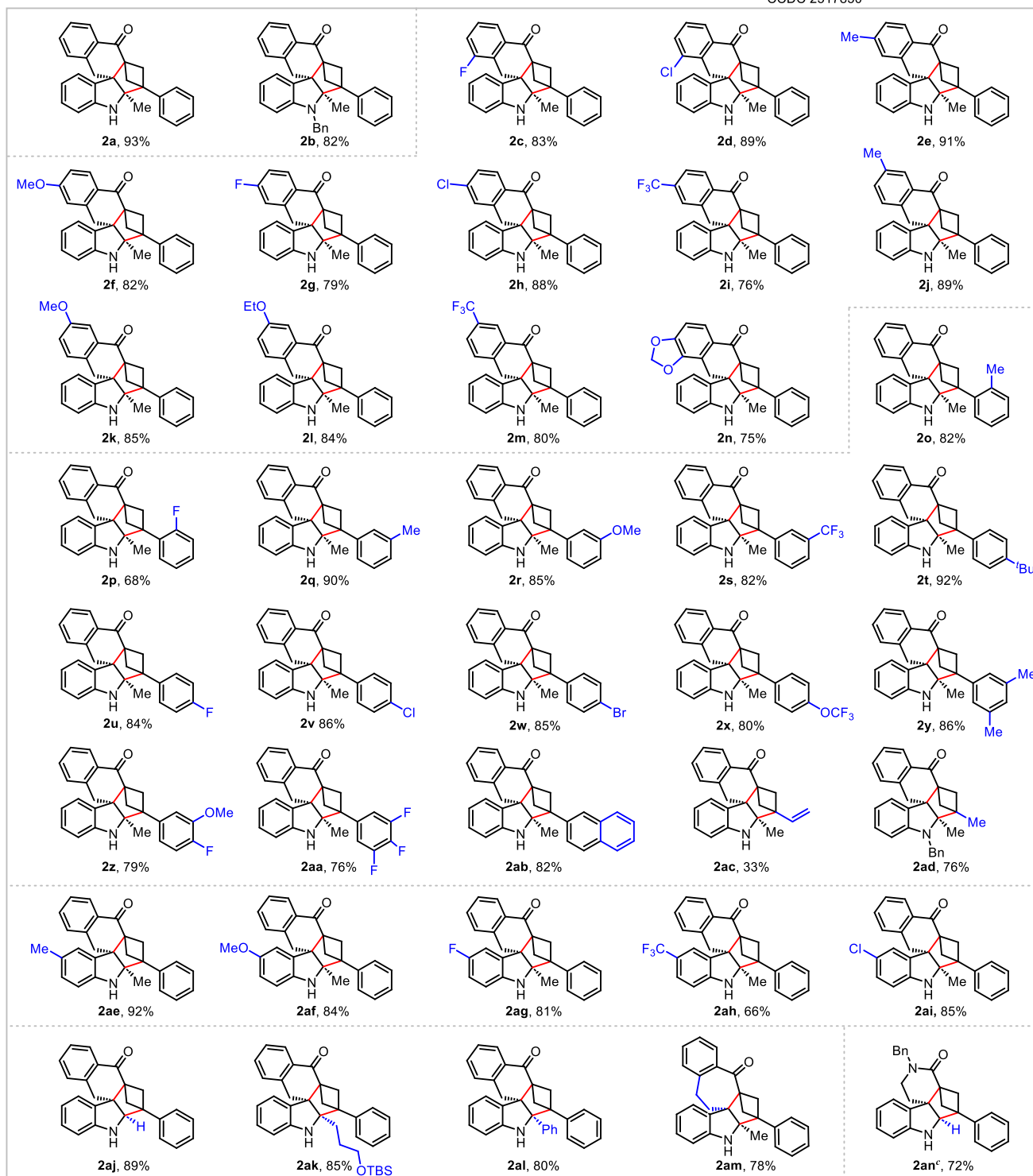
Entry	Deviation from standard conditions	Yield% ^b
1	None	93
2	DCM instead of CH ₃ CN	86
3	HFIP instead of CH ₃ CN	N.D.
4	ⁿ Bu ₄ NBF ₆ instead of ⁿ Bu ₄ NBF ₄	88
5	ⁿ Bu ₄ NI instead of ⁿ Bu ₄ NBF ₄	56
6	Carbon cloth as anode	53
7	Carbon rod as anode	Trace
8	Pt as anode	Trace
9	3 mA instead of 1 mA	92
10	5 mA instead of 1 mA	90
11	No electricity	N.R.
12	Under air	85

^aReaction condition: Undivided cell, graphite felt anode (GF), Pt plate cathode, **1a** (0.20 mmol), ⁿBu₄NBF₄ (0.20 mmol), CH₃CN (4 mL), room temperature, constant current = 1 mA, 1 h, Ar. ^bIsolated yields.





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Scheme 2. Scope of C3-BCB-substituted indoles. ^aReaction conditions: Undivided cell, graphite felt anode (GF), Pt plate cathode, **1a** (0.20 mmol), ⁿBu₄NBF₄ (0.20 mmol), CH₃CN (4 mL), room temperature, constant current = 1 mA, 1 h, Ar. ^bYield of isolated products **2**. ^cThe reaction time is 5 h.



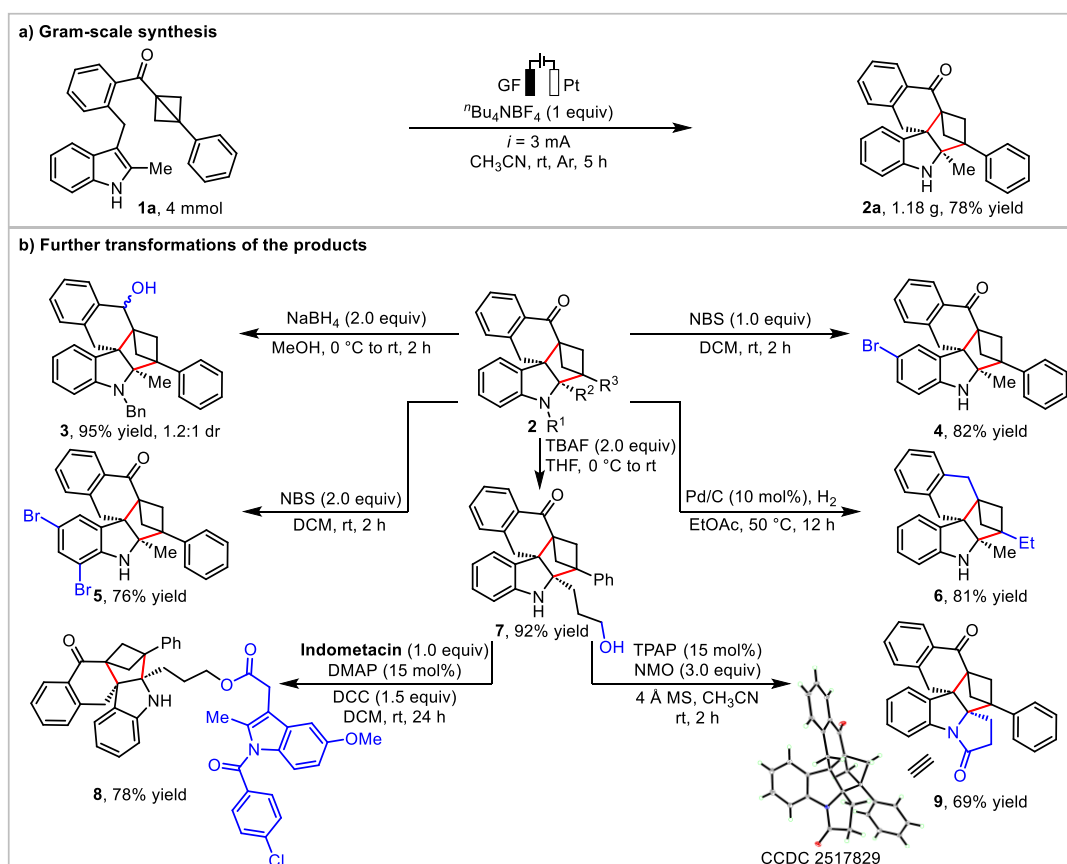
the radical cation-mediated strain-release intramolecular (3+2) cycloaddition reaction may be achieved under mild and sustainable electrochemical conditions. Herein, we report a highly efficient and environmentally friendly electrochemical strategy for the intramolecular (3+2) dearomatization reaction of C3-BCB-substituted indoles, providing access to structurally complex and novel BCH-fused spiroindolines (Scheme 1c). This oxidant-free protocol enables the practical and atom-economic synthesis of a wide range of valuable spirocyclic indolines that bear four contiguous stereogenic centers, including two spiro quaternary carbon stereocenters in generally good yields with a broad substrate scope and functional group compatibility.

Results and discussion

To validate the design strategy for constructing polycyclic spiroindolines, we selected the C3-BCB-substituted indole derivative **1a** as the model substrate and explored a radical cation-mediated strain-release (3+2) cyclization reaction by the electrochemical method. Following systematic optimization, the polycyclic spiroindoline product **2a** was successfully synthesized under a constant current of 1 mA in an undivided cell equipped with a graphite felt anode (GF) and a platinum plate cathode, using acetonitrile as the solvent. The reaction was conducted at room temperature, yielding **2a** in 93% yield (see Table 1, entry 1). First, the screening of solvents indicated the importance of CH₃CN in the

reaction (see Table 1, entries 2 and 3). Additionally, replacing ^tBu₄NBF₄ with ^tBu₄NBF₆ or ^tBu₄NI all resulted in diminished yield (see entries 4 and 5). Electrode screening results indicated that carbon cloth, carbon rod, and Pt plate anodes demonstrated inferior performance compared to the graphite felt anode (see entries 6–8). Considering the crucial role of current in the reaction, increasing the current did not lead to an improvement in yield (see entries 9 and 10). Control experiments confirmed the essential role of electricity, as no reaction was observed in the absence of current (see Table 1, entry 11). Notably, the transformation exhibits low sensitivity to ambient atmospheric conditions, delivering a comparable yield even in the presence of air (entry 12), which underscores the practical value of this protocol. Remarkably, control experiments conducted under conditions adapted from Lewis acid-catalyzed intermolecular reactions demonstrate that the transformation proceeds smoothly with 10 mol% In(OTf)₃ as a Lewis acid catalyst, affording the desired product **2a** in 71% yield (see Table S5 in the SI for more details).

With the optimized reaction conditions established, the substrate scope of this electrocatalytic (3+2) cycloaddition reaction was subsequently explored. As illustrated in Scheme 2. Initially, both unprotected and benzyl-protected BCB-substituted indole compounds **1a** and **1b** could be smoothly transformed into the corresponding spiroindolines **2a** and **2b** in 93% and 86% yields, respectively. Next, we investigated the influence of different substituents on the arene moiety of the aromatic ketone. Under optimal reaction conditions, a range of aromatic ketones bearing



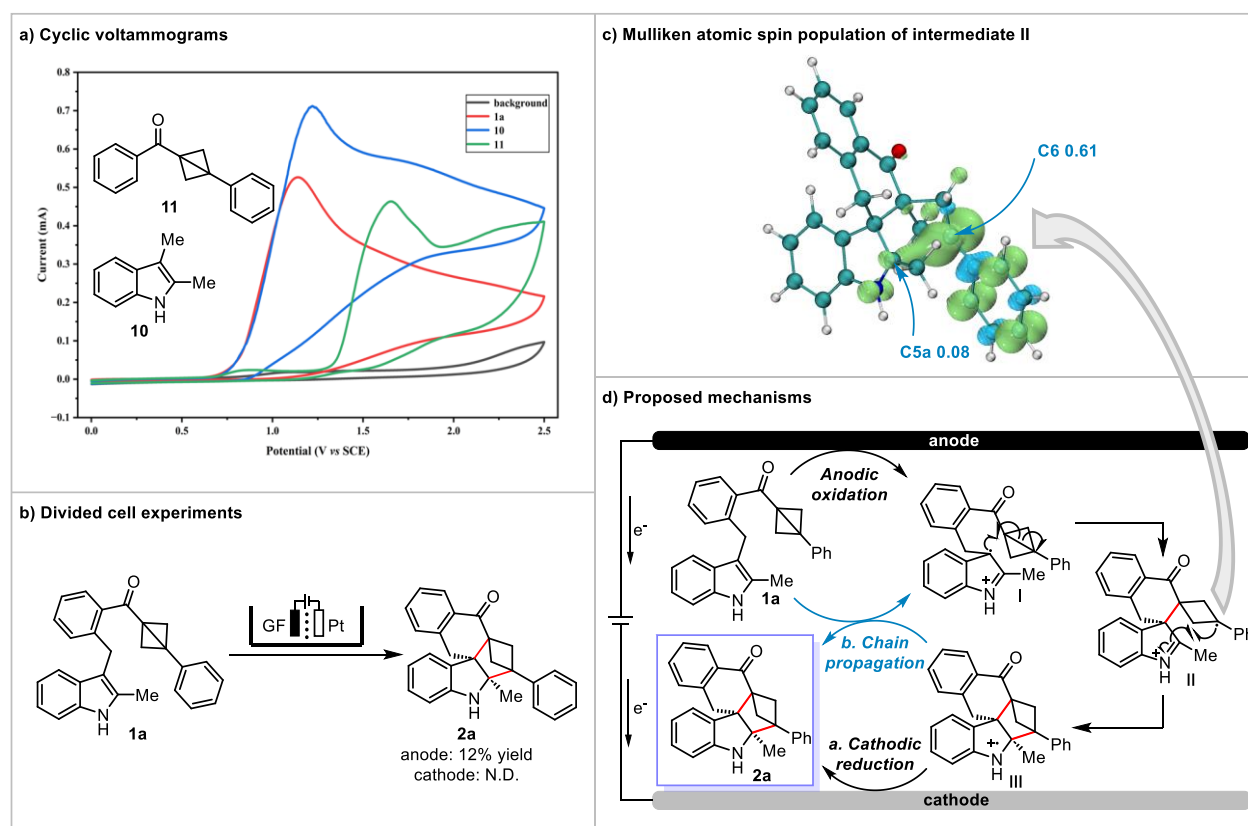
Scheme 3. Gram-scale synthesis and further transformations of the products.



both electron-withdrawing (such as F, Cl, and CF₃) and electron-donating (such as Me, OMe and OEt) substituents at different positions of the aromatic ring can efficiently undergo the reaction, producing the desired products **2c–2m** in 76–91% yields. The structure of compound **2k** was unambiguously verified by crystallographic analysis. In addition, a disubstituted aromatic ketone was applied to the reaction, successfully affording the corresponding polycyclic spiroindoline **2n** in 75% yields. Subsequently, we turned our attention to the R³ moieties on the bridgehead bond in the BCBs. The cycloaddition reaction demonstrated remarkable tolerance toward both electron-deficient and electron-rich substituents at the ortho-, meta- and para-positions of the aromatic ring, including halogen (F, Cl, Br), methyl, tert-butyl, methoxy, trifluoromethoxy, and trifluoromethyl groups. These transformations delivered the desired products **2o–2aa** in 68–92% yields. Replacing the R³ with a 2-naphthyl group was investigated and produced the desired product **2ab** in 82% yield. However, when R³ is a vinyl group, the yield decreases significantly, with the desired **2ac** obtained only in 33% yield. When R³ is a methyl group, the reaction proceeds smoothly, affording the target compound **2ad** in 76% yield. Notably, the reaction of indole derivatives containing a C5-substituent (Me, OMe, F, CF₃, Cl) were also tolerated, producing BCH-fused spiroindolines **2ae–2ai** in 66–92% yields. Furthermore, a variety of functional groups on R² moieties, including an H (as in **2aj**), a silyl ether (as in **2ak**) and a phenyl (as in **2al**) were well tolerated, providing the desired cycloadducts **2aj–2al** in good yields (80–89%). The experimental results indicate that the

R² on the indole ring has no significant effect on the reaction efficiency. More importantly, the homologous substrate with more than one carbon atom also exhibits good compatibility under the optimized reaction conditions, leading to the spirocycloheptane indoline **2am** in decent yield (78%). Interestingly, an amide-linked BCBs **1an** was also well tolerated, affording the desired product **2an** in 72% yield.

To showcase the potential application of this protocol, a scale-up synthesis of **2a** was conducted. Under the standard reaction conditions, 4.0 mmol of BCB **1a** reacted smoothly, resulting in the desired product **2a** in 78% yield (Scheme 3a). Subsequently, we carried out additional late-stage transformations using BCH-fused polycyclic spiroindolines **2** to demonstrate the synthetic utility of these products. First, the carbonyl group of **2b** was reduced to the hydroxyl group with NaBH₄, affording alcohol **3** in high efficiency (95% yield, dr 1.2:1). Furthermore, the spiroindoline **2a** was subsequently elaborated into **4** and **5** via electrophilic aromatic bromination. Interestingly, starting from **2ac**, the carbonyl group and double bond were fully reduced to **6** by Pd/C-catalyzed hydrogenolysis in 81% yield. Next, the silyl group of **2ak** could be removed with TBAF to give the primary alcohol **7**. Alcohol **7** can undergo esterification with indomethacin to afford the complex derivative **8**. Importantly, spiroindoline **7** can also undergo an intramolecular Ley oxidation reaction to access a complex polycyclic spiroindoline **9** containing three spiro carbon stereocenters. The structure of the **9** was unambiguously determined by X-ray crystallographic analysis (Scheme 3b).



Scheme 4. Mechanistic studies and proposed mechanism.



To elucidate the reaction mechanism, we conducted a series of mechanistic investigations (see Supporting Information for details). Upon the introduction of TEMPO (2,2,6,6-tetramethylpiperidoxyl) or BHT (butyl-hydroxytoluene) as radical scavengers, the formation of the product was almost entirely suppressed. Furthermore, mass spectrometric analysis identified adducts between compound **1a** and both TEMPO and BHT. These findings suggest that the reaction mechanism likely involves a radical pathway. Similarly, when C2-unsubstituted **1an** was used as the substrate and P(OEt)₃ as a trapping reagent, the desired product **2an** was obtained in 38% yield. Meanwhile, an indole phosphorylation product was detected by HRMS, indicating the presence of a radical cation intermediate in the reaction (see Supporting Information for details). Furthermore, according to cyclic voltammetry (CV) experiments, the oxidation peaks of **1a** and its decomposition product, 2,3-dimethylindole **10**, with BCB **11** were observed at +1.14 V, +1.22 V, and +1.66 V (vs. SCE), respectively (Scheme 4a). These results indicate that the oxidation potential of compound **1a** is primarily attributed to the indole moiety, further suggesting that the reaction is likely initiated from the indole. Notably, the results from the divided-cell experiment revealed that the target product **2a**, with a 12% yield, was detected in the anode compartment during substrate decomposition, whereas no reactions occurred in the cathode compartment (Scheme 4b). Importantly, the Faradaic efficiency reveals that only 0.2 equiv of charge is sufficient to achieve complete conversion (see Supporting Information for details). This finding indicates that the reaction not only involves cathodic reduction but may also undergo chain propagation reactions.

According to the above studies and literature reports,⁵⁸⁻⁶¹ a possible mechanism for the electrochemical dearomative (3+2) annulation of indole derivatives was proposed in Scheme 4d. To begin with, compound **1a** undergoes anodic oxidation to generate the radical cation intermediate **I**. Subsequently, the intramolecular radical promotes the ring-opening of BCB, converting **I** into the benzyl radical species **II**. To validate the proposed intermediate, spin density analysis of radical cation **II** was performed. The results show that the unpaired electron is highly localized at the C6 position (Mulliken spin population 0.61), while the spin density at C5a is negligible (0.08), indicating that intermediate **II** is a C6-localized radical, consistent with our hypothesis (Scheme 4c). Then, intermediate **II** undergoes an intramolecular radical addition cyclization to afford radical cation **III**. Ultimately, cathodic reduction or chain propagation of intermediate **III** delivers the target polycyclic spiroindolines.

Conclusions

In conclusion, we have developed a highly efficient and environmentally friendly electrochemical-driven radical cation-mediated strain-release dearomative (3+2) cyclization of C3-BCB-substituted indoles. Through this methodology, a series of structurally novel and densely functionalized BCH-fused spiroindolines was successfully synthesized as single diastereomers with good yields. This method involves mild conditions and produces BCH-fused spiroindolines with a broad substrate scope and functional group compatibility as well as potential application, as demonstrated by late-stage synthetic transformations. Mechanistic studies provided strong evidence for a radical process. This practical and sustainable method is anticipated to see broader applications in organic synthesis and medicinal chemistry.

Author contributions

Y. Zhu, E. Pu and S. Yang designed and performed the experimental work. D. Zhao performed calculations. Q. Xu, P. Jiang, and X. Li contributed to the analysis and interpretation of data. H. Zhang and J. Chen conceived the project. J. Chen and Y. Zhu wrote the manuscript. All authors contributed to or approved the final version of the paper.

Conflicts of interest

There are no conflicts to declare.

Data availability

Experimental procedures, crystallographic data, compound characterization data, and copies of NMR spectra of the products are available as a PDF file.

Acknowledgements

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Experimental procedures, crystallographic data, compound characterization data and copies of NMR spectra of the products are provided in the Supporting Information.

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