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Divergent reactions of indolyl vinyl isonitriles: A facile access to skeletally diverse carboline-based biheteroaryls

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ABSTRACT

Skeletal transformations of heteroaromatic compounds *via* endocyclic bond cleavage have emerged as powerful tools in modern organic synthesis. Nonetheless, selective cleavage of the C2–N1 bond in indoles without the assistance of metal reagents or additives remains highly challenging, owing to the strong aromatic stabilization and intrinsic bond strength of the indole framework. Herein, we present a distinctive dimerization of C3-substituted indolyl vinyl isonitriles that proceeds through a sequential "head-to-head" cross-coupling, pyridannulation, and C2–N1 bond cleavage cascade. This transformation not only disrupts the indole core but also forges a new pyridine ring, thereby providing a metal-free and efficient route to highly functionalized 1-(2-pyridyl)-β-carbolines. Notably, an oxidative aromatic dimerization of C3- and C2-substituted heteroaryl vinyl isonitriles was developed, providing a modular route to bis-β-carbolines, bis-γ-carbolines, and their chalcogen analogues.

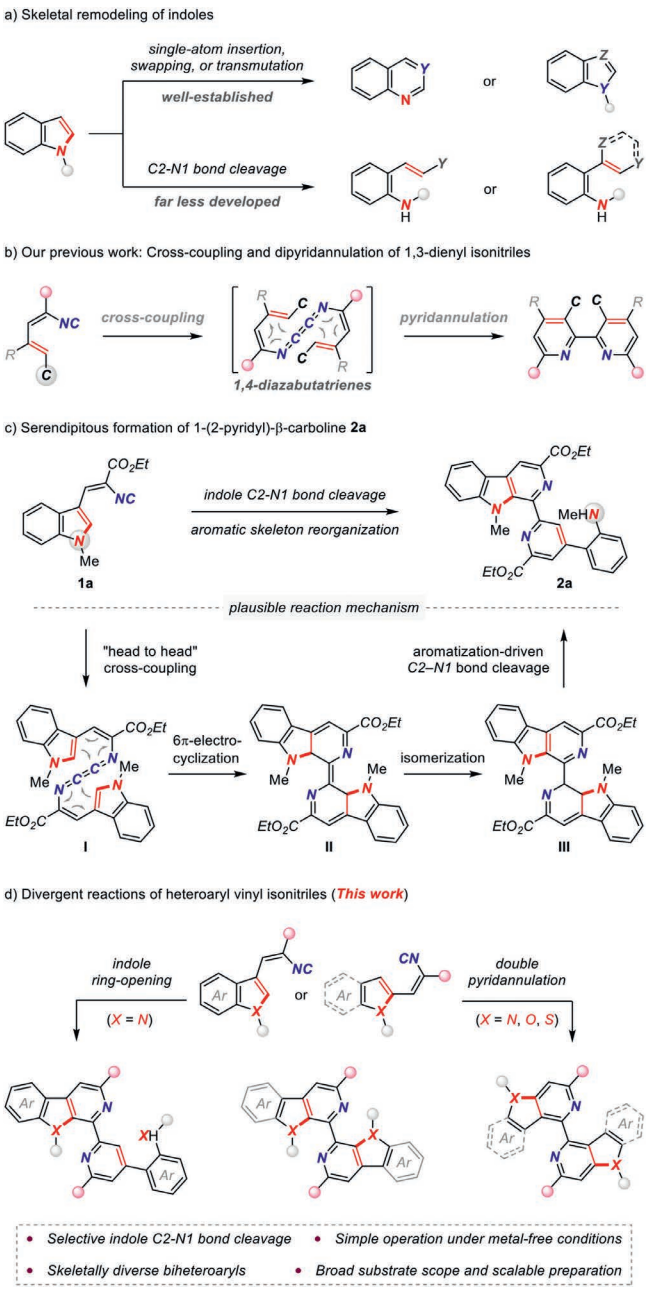
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The skeletal remodeling of heterocyclic cores provides new avenues for molecular design and has recently become a promising, though challenging, frontier in synthetic chemistry [1–5]. Among various heterocycles, indoles have received considerable attention, with numerous strategies developed to achieve structural diversification and novel functionality through single-atom insertion [6–11], swapping, or transmutation (Scheme 1a) [12–17]. These methods serve as powerful complements to traditional peripheral modifications, such as C-H functionalization [18,19] or dearomative cyclization [20,21]. However, transformative reactions in indoles that enable selective cleavage of the inert C2–N1 bond, accompanied by aromatic framework reorganization through a green and sustainable strategy, remain scarce and certainly highly desirable [22–26]. This is largely due to the high aromatic stability of the pyrrole ring and the poor leaving-group ability of the amino anion [6,27,28]. In this regard, the seminal studies by Studer [23], Lu [24], and Park [29] demonstrated transition-metal-free skeletal reorganization of indoles into anilines, quinoxaline, or *meta*-substituted pyridines *via* C2–N1 bond cleavage, achieved through silyl anion addition [23], an isodesmic reaction strategy [24], or the use of *in situ*–generated enamines as key intermediates [29]. Despite these advances, the development of new strategies for C2–N1 bond cleavage and aromatic skeleton reorganization, without reliance on metal reagents or additional additives, remains a compelling yet underexplored area of research [30–36].

Isonitriles are versatile building blocks for the construction of a wide range of azaheterocycles [37–40], and our group has maintained a long-standing interest in isonitrile dimerization chemistry [41–48]. Recently, we developed a novel strategy for synthesizing a broad array of 2,2′-bipyridines *via* the thermal dimerization of 1,3-dienyl isonitriles through a "head-to-head" cross-coupling and dipyridannulation process (Scheme 1b) [47]. In an effort to expand the scope of this dimerization reaction, indolyl vinyl isonitrile **1a** was subjected to similar conditions. Unexpectedly, a novel product, 1-(2-pyridyl)-β-carboline **2a**, was formed via a remarkably facile cascade featuring C2–N1 bond cleavage of the indole and reorganization of the aromatic skeleton (Scheme 1c). The reaction starting with a "head-to-head" cross-coupling of indolyl vinyl isonitriles, yielding a 1,4-diazabutatriene intermediate (**I**) [41,49–50]. Then, intermediate **I** undergoes a spontaneous 6π-electrocyclization process to yield the bis-dihydro-β-carboline intermediate **II** and its isomer **III** formed *via* a proton shift. Finally, aromatization serves as a driving force to promote the C-N

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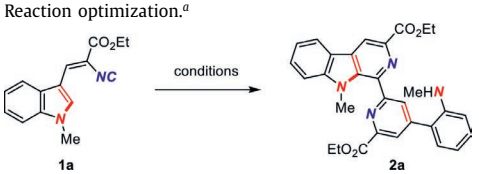
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Scheme 1. Divergent reactions of heteroaryl vinyl isonitriles.

bond cleavage [22,51] to furnish the final product **2a**. Particularly, biheteroaryls are important structural motifs known for their diverse biological and physical properties, and are widely present in bioactive compounds, pharmaceuticals, organic functional materials, metal ligands, and natural products [52,53]. Among them, carboline-based biheteroaryls hold particular importance due to their prominent role in medicinal chemistry, especially as antitumor agents [54–58]. Hence, there is a strong demand for the development of new, efficient, and broadly applicable methodologies to access to these structurally diverse scaffolds [59–61]. Thus, this serendipitous observation prompted a more detailed investigation. Herein, we disclose an unprecedented dimerization of heteroaryl vinyl isonitriles that enables selective indole C2−N1 bond cleavage or oxidative aromatic dimerization, thereby offering a switchable strategy for the divergent synthesis of structurally diverse 1-(2-pyridyl)-β-carbolines, bis-β-carbolines, bis-γ-carbolines, and their chalcogen analogues (Scheme 1d).

Table 1
Reaction optimization.[a]



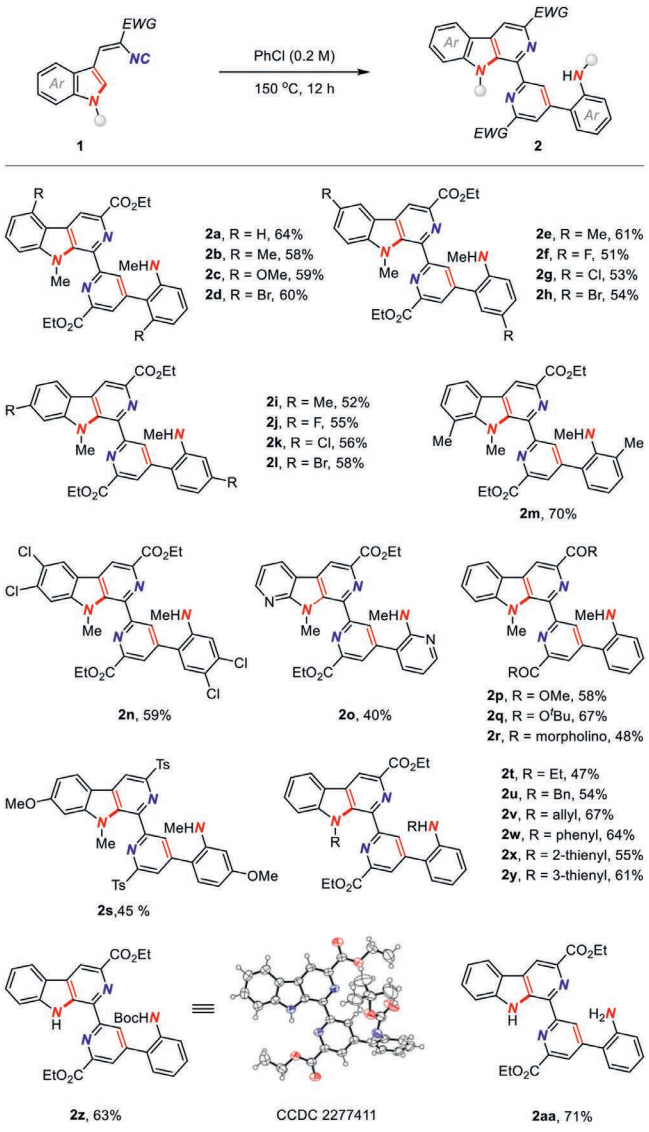
Entry	Temp (°C)	Solvent	Time (h)	Conv. (%)	Yield of **2a** (%)[b]
1	150	PhCl	12	93	57
2	150	PhMe	12	45	21
3	150	MeCN	12	34	28
4	150	DCE	12	52	34
5	150	DME	12	75	44
6	150	DMF	12	92	55
7	150	EtOH	12	59	34
8	130	PhCl	12	64	44
9	170	PhCl	12	99	54
10[c]	150	PhCl	12	99	56
11[d]	150	PhCl	12	97	66 (64)[f]
12[e]	150	PhCl	12	92	56

[a] Reaction conditions: **1** (0.2 mmol) in solvent (c = 0.1 mol/L) at 130−170 °C for 12 h.
[b] Yields were determined by ^{1}H NMR analysis of the crude reaction mixture using dibromomethane as an internal standard.
[c] c = 0.3 mol/L.
[d] c = 0.2 mol/L.
[e] c = 0.05 mol/L.
[f] Isolated yields.

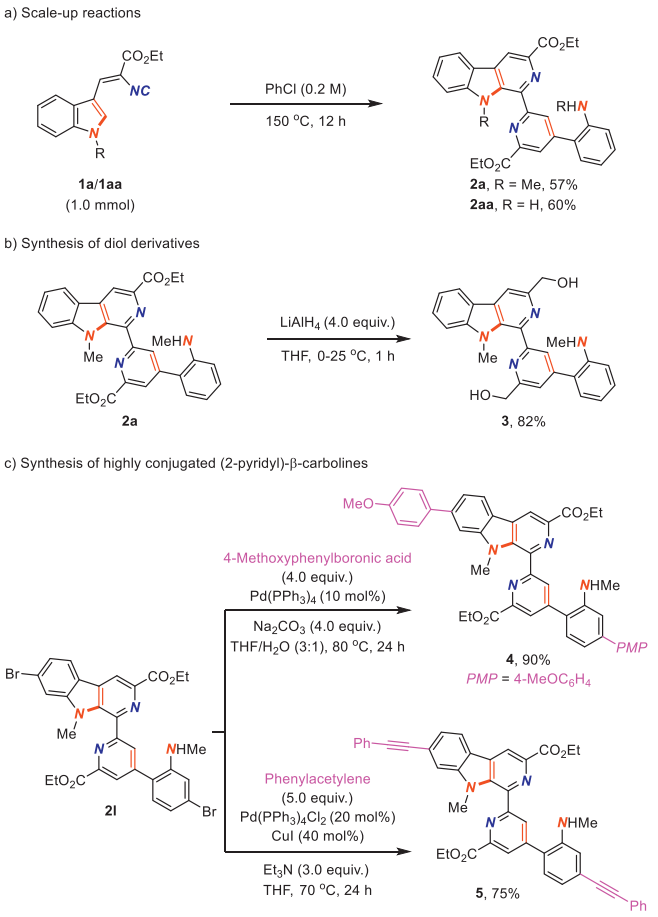
Since the standard reaction conditions of our previous report provided the desired product 1-(2-pyridyl)-β-carboline **2a** in 57% yield (Table 1, entry 1) [47], we further optimized the reaction conditions to improve the yield of the product. Variation of solvents (PhMe, MeCN, DCE, DME, DMF, and EtOH) did not lead to higher yields (Table 1, entries 2−7). After carefully examining reaction temperature and concentration, we found that PhCl (0.2 mol/L) at 150 °C provided **2a** in up to 66% yield (Table 1, entries 8−12). Accordingly, the conditions in entry 11 were identified as optimal (see Supporting information for details).

Next, we examined the generality of this protocol with a broad range of C3-substituted indolyl vinyl isonitriles. As shown in Scheme 2, the influence of substituents on the indole benzene ring was first investigated. Electron-donating groups (−Me, −OMe) and halogens (−F, −Cl, −Br) at different positions reacted smoothly to afford the corresponding products **2a**−**2m** in satisfactory yields, demonstrating the wide applicability of this transformation. Multiple substituents on the benzene ring were also tolerated (**2n**). Notably, a C3-azaindolyl vinyl isonitrile proved suitable, providing **2o** in moderate yield. Furthermore, indolyl vinyl isonitriles bearing carbomethoxy (−CO_2Me), *tert*–butoxycarbonyl (−$CO_2{}^t$Bu), amide (−CON(C_2H_4)$_2$O), and tosyl (−Ts) groups readily underwent the cascade cyclization/ring-opening process, affording 1-(2-pyridyl)-β-carbolines **2p**−**2s** in moderate yields. Variation of the *N*-substituent on the indole was also well tolerated: ethyl (−Et), benzyl (−Bn), allyl (−$CH_2CH{=}CH_2$), aryl (−Ph), heteroaryl (2-thienyl, 3-thienyl), and *tert*–butoxycarbonyl (−Boc) groups all furnished the desired products **2t**−**2z** in moderate yields, highlighting the excellent functional group compatibility of this method. The structures of **1e** (CCDC: 2499375) and **2z** (CCDC: 2277411) were unambiguously confirmed by X-ray crystallographic analysis. Remarkably, even *N*-unsubstituted indolyl vinyl isonitrile participated efficiently, affording **2aa** in moderate yield and highlighting the broad synthetic utility and generality of this protocol.

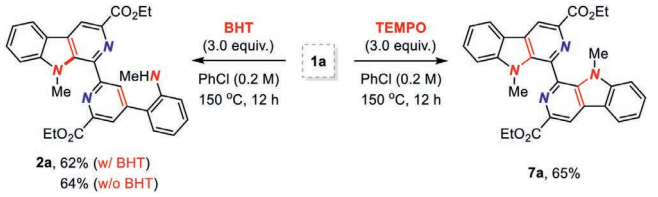
To demonstrate the practical utility of this strategy, the protocol was successfully applied to the scale-up synthesis of **2a** and



Scheme 2. Substrate scope of 1-(2-pyridyl)-β-carbolines. Reaction conditions: **1** (0.2 mmol) in PhCl (1 mL) at 150 °C for 12 h. Isolated yields.



Scheme 3. Scaled-up preparation and post-synthetic modifications.

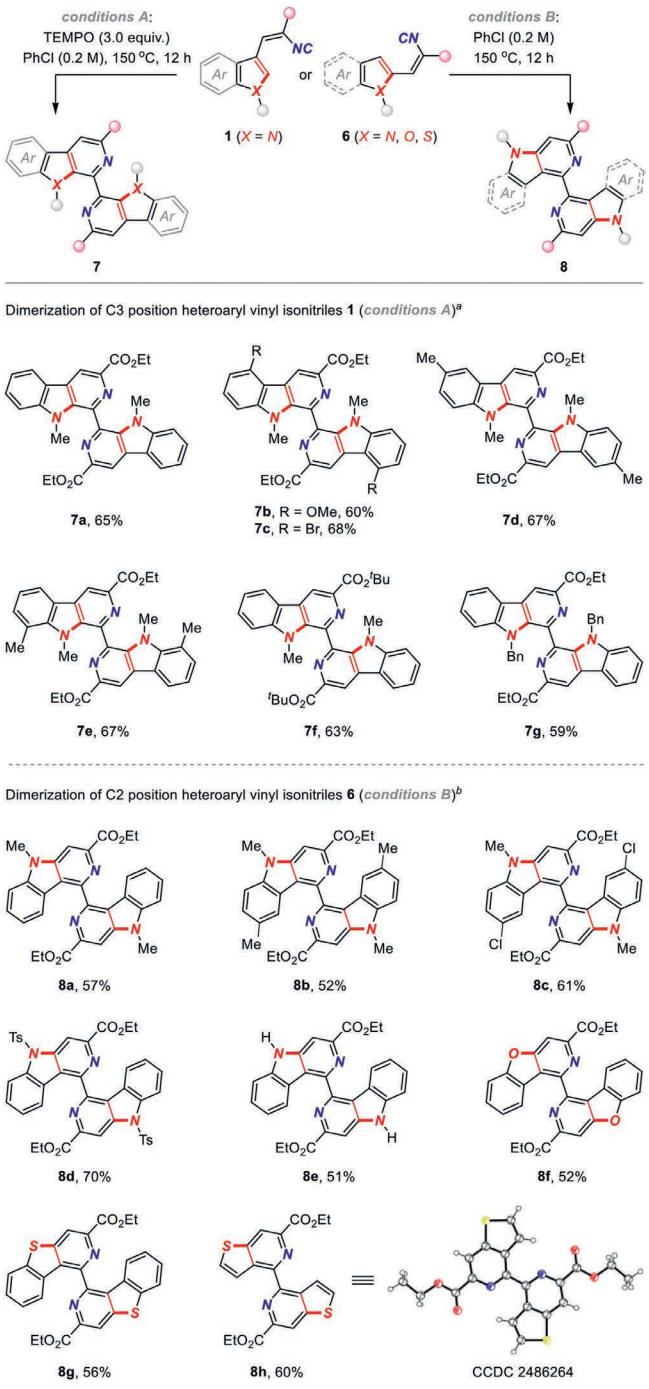


Scheme 4. Control experiments and oxidative aromatization. Reaction conditions: **1a** (0.2 mmol) and radical scavenger (0.6 mmol) in PhCl (1 mL) at 150 °C for 12 h. Isolated yields.

2aa, with only a slight decrease in yield, underscoring its suitability for larger-scale applications (Scheme 3a). The synthetic versatility of 1-(2-pyridyl)-β-carbolines was further showcased through post-synthetic derivatizations. For example, reduction of the two ester groups in derivative **2a** with $LiAlH_4$ under mild conditions efficiently delivered diol **3** in high yield (Scheme 3b) [62]. Moreover, Pd-catalyzed cross-coupling of **2l** furnished π-conjugated (2-pyridyl)-β-carbolines **4** and **5** in excellent yields, bearing *p*-methoxyphenyl and phenylethynyl substituents on their conjugated backbones, respectively (Scheme 3c) [63,64].

Under the optimized conditions, the ring-opened intermediate could not be detected. To gain deeper insight into the reaction mechanism, a series of control experiments was conducted (Scheme 4). The addition of 2,6-di–*tert*–butyl–4-methylphenol (BHT) as a radical scavenger only slightly affected the reaction, affording **2a** in 62 % yield. This observation suggests that the ring-opening process likely proceeds *via* an ionic rather than a radical pathway. In contrast, the addition of 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO), another radical scavenger, suppressed the formation of **2a** and instead promoted oxidative aromatization, giving **7a** in 65 % yield (see Supporting information for details). This outcome indicates that TEMPO acted as a commercially available oxidant rather than simply trapping radicals to generate a bis-β-carboline product [65,66]. Collectively, these findings support the notion that aromatization serves as the driving force for C2−N1 bond activation, consistent with the proposed pathway involving C2−N1 bond cleavage and aromatic framework reorganization [22,51].

Motivated by these findings, we explored the substrate scope, focusing on bis-β-carbolines **7** and other structurally related biheteroaryls. As illustrated in Scheme 5, treatment of C3-substituted indolyl vinyl isonitriles **1** with TEMPO in PhCl under reflux afforded the corresponding bis-β-carboline products **7a**–**7g** in moderate yields (59 %–68 %). We next investigated ethyl (*Z*)-2-isocyano-3-(1-methyl-1*H*-indol-2-yl)acrylate (**6a**), which underwent direct dimerization to afford bis-γ-carboline **8a** as the sole product, without bond cleavage (see Supporting information for details). The observed difference in selectivity between C3- and C2-indolyl vinyl isonitriles can be attributed to the distinct bond dissociation energies (BDEs) of intermediates **III** and **III′** (Figs. S1 and S2 in Supporting information). The C2–N1 bond in **III** is substantially weaker



Scheme 5. Synthesis of bis-β-carbolines, bis-γ-carbolines, and their chalcogen analogues. [a] Reaction conditions A: **1** (0.2 mmol) and TEMPO (0.6 mmol) in PhCl (1 mL) at 150 °C for 12 h. [b] Reaction conditions B: **6** (0.2 mmol) in PhCl (1 mL) at 150 °C for 12 h. Isolated yields.

(BDE = 47.7 kcal/mol) than the corresponding bonds in **III′** (C(sp^3)–C(sp^2): 77.8 kcal/mol; C2–N1: 96.6 kcal/mol). Consequently, cleavage of the C(sp^3)–C(sp^2) or C2–N1 bond in **III′** is disfavored, this intermediate preferentially undergoes oxidative aromatization under aerobic conditions. The scope of this transformation was further established with C2-indolyl vinyl isonitriles **6**. Substrates bearing electron-donating (–Me) or halogen (–Cl) substituents on the indole ring smoothly delivered the desired products **8b**–**8c** in moderate yields. The *N*-Ts substituent on the indole core was also compatible, affording **8d** in good yield. Even the unsubstituted indole underwent smooth conversion, providing **8e** in moderate yield. Notably, the reaction could be further extended to other C2-substituted heteroaryls, including benzofuran, benzothiophene, and thiophene, which furnished the corresponding products **8f**–**8h** in moderate yields, thereby highlighting the broad functional-group tolerance of this protocol. The structures of **6g** (CCDC: 2499374) and **8h** (CCDC: 2486264) were unambiguously confirmed by X-ray crystallographic analysis.

In conclusion, we have developed a distinctive, metal-free dimerization strategy for synthesizing 1-(2-pyridyl)-β-carbolines from C3-indolyl vinyl isonitriles through an unprecedented ring-opening pyridannulation process. In addition, an oxidative aromatic dimerization of C3- and C2-substituted heteroaryl vinyl isonitriles has been established, enabling access to diverse carboline-based biheteroaryls, including bis-β-carbolines, bis-γ-carbolines, and their chalcogen analogues. Collectively, this work not only expands the scope of isonitrile dimerization chemistry but also establishes a versatile platform for the synthesis and discovery of novel bioactive biheteroaryls. Further studies are underway to broaden the applicability of this methodology to additional heterocyclic frameworks.

CRediT authorship contribution statement

Yu Liu: Methodology. **Lan Bao:** Methodology. **Xiang Lyu:** Methodology. **Zhonglin Wang:** Methodology. **Zhengrun Chen:** Methodology. **Jinhuan Dong:** Methodology. **Xianxiu Xu:** Writing – review & editing, Conceptualization. **Zhongyan Hu:** Writing – review & editing, Writing – original draft, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2025.112201.

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