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RESEARCH ARTICLE

View Article Online
View Journal | View Issue

Cite this: *Org. Chem. Front.*, 2025, **12**, 4209

Electrochemical [3 + 2]/[4 + 2] cyclization to indole-fused polycyclics†

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Received 20th February 2025,
Accepted 20th March 2025

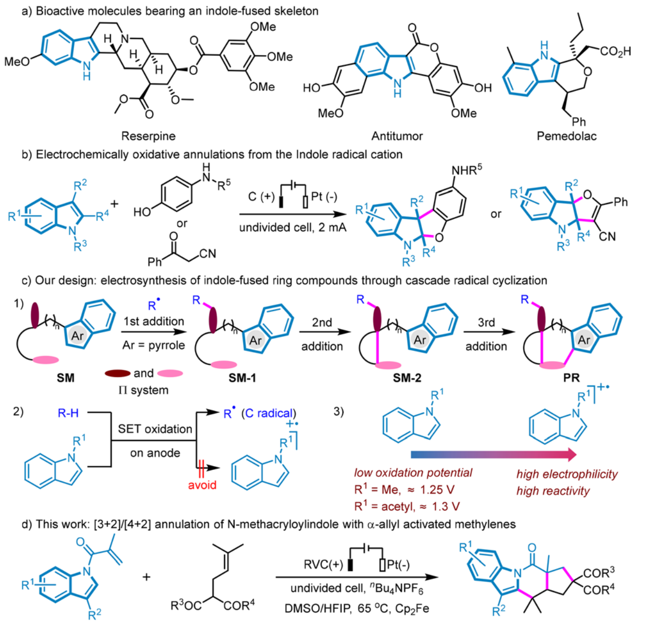
DOI: 10.1039/d5qo00353a

rsc.li/frontiers-organic

The preparation of highly complex indole-fused polycyclics has been in high demand because of their many biological activities. The electrochemical coupling of the radical intermediates with adjacent indole rings has been recognized as a green, straightforward, and powerful methodology for constructing these compounds. Electrochemical coupling is characterized by high atom and step economy under mild and exogenous oxidant-free conditions I. However, this methodology is also challenging and underdeveloped because of the low oxidation potential of indole rings, which, therefore, easily decompose under electrolysis conditions. Herein, we report straightforward electrosynthesis of indole-fused polycyclics achieved by carrying out radical domino couplings between *N*-methacryloylindoles and α-allyl-substituted methylenes. This electrolysis proved to be efficient in open air with good functional group tolerance, which meant that stringent removal of H_2O and oxygen was not necessary.

Indole-fused polycyclics display attractive and diverse biological activities, and they are prevalent in pharmaceuticals and natural products (Scheme 1a).[1] Thus, developing straightforward, efficient, and sustainable synthetic methods for preparing these scaffolds has been in high demand. Meanwhile, the quest for swift construction of highly complex and unprecedented molecular scaffolds, including indole-fused polycyclics, has attracted the wide and sustained attention of synthetic organic, pharmaceutical and material chemists.[2] Radical-initiated domino cyclization *via* multiple additions across unsaturated bonds, including those of alkenes,[3] alkynes,[4] cynaides,[5] and isocyanides,[6] have long been pursued and developed as a relatively straightforward and efficient strategy that avoids multistep pre-functionalization and features high step and atom economy. In this context, some cyclization cascades to fused polycyclics, including indole-fused systems from N-,[7] S-,[8] or C-centered[9] radicals, have been developed,[10] but the use of transition metal catalysts or stoichiometric oxidants or the preparation of pre-activated precursors is usually unavoidable. Therefore, it is appealing to develop a greener and more economical strategy for synthesizing indole-fused systems.

Electrosynthesis has emerged as a greener tool in redox processes eliminating the need for oxidizing or reducing reagents —and thereby, with a higher atom economy, reducing the generation of the undesirable byproducts and the associated



Scheme 1 Importance and construction of indole-fused polycyclics.

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† Electronic supplementary information (ESI) available. CCDC 2422567. For ESI and crystallographic data in CIF or other electronic format see DOI: **https://doi.org/10.1039/d5qo00353a**

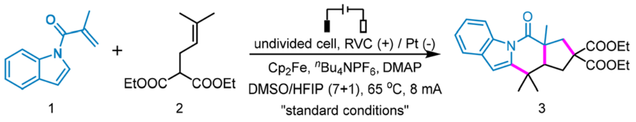
hazards.[11] In addition, organic electrochemistry has been widely used as a powerful tool to synthesize highly complex fused systems through radical domino couplings.[12] Our group also reported many electrosyntheses of fused systems, including polycyclic N-heteroaromatics,[13] O-heteroaromatics,[14] S-heteroaromatic compounds,[15] and fused systems bearing a saturated carbocyclic ring[16] *via* radical domino cyclization. Indole-fused polycyclics could also be electrochemically synthesized from the N-centered radical-initiated domino cyclization.[17]

Moreover, additional ring fusion of indoles could lead to the formation of the corresponding indole-fused architectures through the electrochemical oxidative annulations from the indole radical cations, with these radical cations generated smoothly and easily on the anode because of their lower oxidation potentials (Scheme 1b).[18] Here, we designed a straightforward electrosynthesis of indole-fused systems *via* a three-step radical addition (Scheme 1c-1). The C-centered radical was generated from the single-electron transfer (SET, Scheme 1c-2) and engaged with π systems to obtain the corresponding radical adducts (**SM-2**). Finally, the coupling of the radical with adjacent indole rings led to the formation of the desired fused systems (**PR**). It is extremely challenging to achieve this transformation, because the indole rings feature low oxidation potential and can be easily oxidized to the corresponding radical cations (Scheme 1c-3). The generated indole radical cations possess high electrophilicity and reactivity and can be transformed into oxidation,[19] oxidative coupling,[20] oxidative ring opening,[21] oxidative cyclization,[22] and oxidative ring opening and cyclization products.[23]

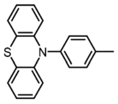
To our delight, an electrochemical [3 + 2]/[4 + 2] cyclization of *N*-methacryloylindoles with α-allyl-activated methylenes to produce indole-fused polycyclics was successfully developed (Scheme 1d). Cp_2Fe was used as a catalyst to promote this transformation and prevent the oxidative decomposition of indole starting materials and products attributed to the low oxidation potential of Cp_2Fe.

At the outset, considerable efforts were devoted to screening of a range of electrolysis parameters (Table 1 and Tables S1, S2, S3, S4 in the ESI†). To our delight, the desired product was acquired in 75% yield using Cp_2Fe as the redox catalyst, DMAP as the base additive in a mixed DMSO/HFIP (7/1, 8 mL) solvent under a constant current of 8 mA at 65 °C in an undivided cell equipped with a reticulated vitreous carbon (RVC) anode and a platinum cathode (entry 1). The use of HFIP as the co-solvent was crucial; it might have enhanced the stability of the radical cations and their oxidative stability.[24] Notably, no target product was detected in the absence of Cp_2Fe (entry 2). Using other commercially available and synthesized organic redox catalysts with similar or higher oxidation potentials including TEMPO, DDQ and other substituted 10-phenyl-10*H*-phenothiazine (PTH) species almost completely prevented the formation of the desired product (entries 4 and 5). No desired product was detected when $FeCl_2$ or $Fe(OAc)_2$ was used as the catalyst instead of Cp_2Fe, with reduction product generated on the cathode (entry 6). This electrosynthesis was also completely

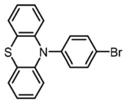
Table 1 Optimization of reaction conditions[a]



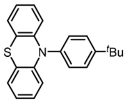
Entry	Variation from "standard conditions"	Yield[b] (%)
1	None	75
2	No Cp_2Fe	0
3	No DMAP	18
4	With TEMPO or DDQ as catalyst instead of Cp_2Fe	0, 0
5	With **C-1**, **C-2**, **C-3**, **C-4** as catalyst instead of Cp_2Fe	Trace, 0, trace, trace
6	With $FeCl_2$ or $Fe(OAc)_2$ as catalyst instead of Cp_2Fe	0, 0
7	With $Cu(OAc)_2$, $CuBr_2$, $Cu(NO_3)_2$ or $CuCl_2$ as catalyst instead of Cp_2Fe	0, 0, 0, 0
8	With $Ni(OAc)_2$, $NiBr_2$, $NiCl_2$, $Ni(SO_4)_2$ as catalyst instead of Cp_2Fe	0, 0, 0, 0
9	With MnO_2, $MnBr_2$, $Mn(OAc)_2$, $MnCl_2$ as catalyst instead of Cp_2Fe	0, 0, 0, 0
10	Pyridine or *N*,*N*-dimethylaniline instead of DMAP	<15
11	At 50 °C or 80 °C	72, 57
12	Under N_2	65
13	No current	0



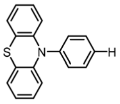
C-1



C-2



C-3

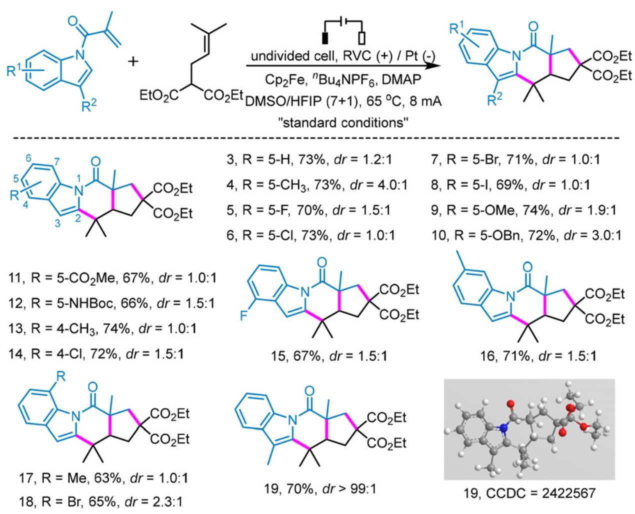


C-4

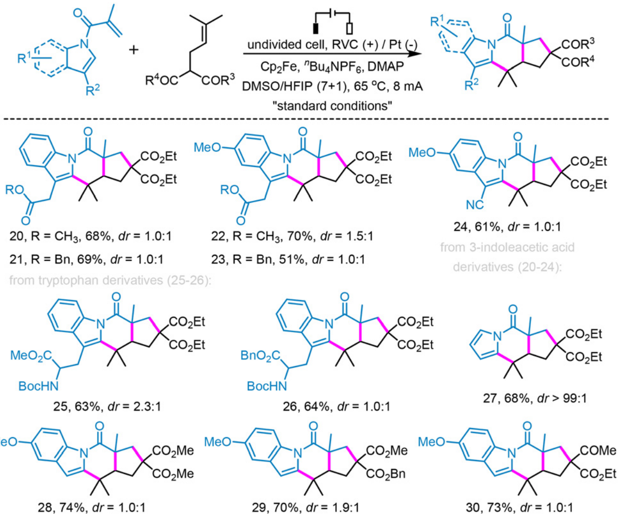
[a] Reaction conditions: *N*-methacryloylindole **1** (0.3 mmol, 55.5 mg), α-allyl-activated methylene **2** (0.75 mmol, 171.1 mg), Cp_2Fe (0.15 mmol, 27.9 mg), DMAP (0.3 mmol, 36.6 mg), $^nBu_4NPF_6$ (0.6 mmol, 232.2 mg), DMSO/HFIP (7/1, 8 mL), 65 °C, 8 mA, 3–4 h, 2.99–3.99 F mol^{-1}, undivided cell, RVC anode (100 PPI, 10 mm × 10 mm × 12 mm), platinum plate cathode (10 mm × 10 mm × 0.1 mm). Cp_2Fe: ferrocene, TEMPO: 2,2,6,6-tetramethylpiperidinooxy; DDQ: 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; DMSO: dimethyl sulfoxide; DMF: *N*,*N*-dimethylformamide; HFIP: 1,1,1,3,3,3-hexafluoro-2-propanol. [b] Yields determined using HPLC analysis with **3** as the external standard.

supressed when Cp_2Fe was replaced by a species containing another transition metal, including Cu, Mn, or Ni salt (entries 7–9). A dramatic decrease of the yield was also observed in the absence of DMAP (entry 3). Replacing DMAP with pyridine or *N*,*N*-dimethylaniline resulted in a dramatic yield reduction (entry 10). A comparable yield was obtained at a lower temperature of 50 °C. However, a negative effect was observed at a higher temperature (entry 11). A 65% yield was obtained under N_2, which revealed that stringent removal of oxygen was not necessary (entry 12). A control experiment indicated that electricity was indispensable (entry 13).

Substrate scope was investigated by varying the indole rings and activated methylenes (Schemes 2 and 3). To our delight, these electrochemical [3 + 2]/[4 + 2] cyclization cascades to N-hetero fused polycyclics demonstrated broad tolerance toward a series of substituents at the C5 (**3–12**), C4 (**13–15**), C6 (**16**), C7 (**17**, **18**), and C3 (**19–21**, **25**, **26**) positions of the indole ring. Moreover, good functional group tolerance was observed, including for H (**3**), alkyl groups (**4**, **13**, **16**, **17**, **19**), halogens (**5–8**, **14**, **15**, **18**), OMe (**9**, **22–24**, **28–30**), OBn (**10**), CO_2Me (**11**, **20**, **22**, **25**), CO_2Bn (**21**, **23**, **26**), NHBoc (**12**, **25**, **26**), and CN (**24**). Notably, this electrochemical cyclization exhibited excellent tolerance of halogens as no dehalogenation byproducts were detected, even when iodine was involved (**8**). Furthermore, it was also compatible with Boc, commonly used as protective group of the N–H bond. The electron-rich indole rings were found to show higher reactivity. However, the indole ring substituted with a highly electron-withdrawing group, including CF_3 and NO_2, was unreactive. Furthermore, this electrosynthesis proceeded smoothly with a good yield when the substrate was substituted with both an electron-withdrawing group and electron-donating group (**24**). A good yield was obtained when naturally derived *N*-methacryloylindole was used (**20–26**). Replacing the indole ring with pyrrole was also compatible (**27**). Excellent reaction compatibility was obtained when another activated methylene was involved, including dimethyl malonate (**28**), benzyl acetylacetate (**29**), and ethyl acetoacetate (**30**). Unfortunately, no desired product was formed when α-allyl-activated methylene with monosubstituted or unsubstituted group next to the alkene was investigated (Scheme S1, ESI,† **M1–M3**). Replacing alkyl on the ester group with an aryl group also resulted in no product (**M4**). These results might have been due to the instability or steric hindrance of the corresponding alkyl radical intermediate. A gram-scale synthesis was performed to demonstrate the application potential of this electrochemical [3 + 2]/[4 + 2] annulation to N-hetero fused polycyclics. To our delight, a similar yield (64% isolated yield) was obtained (Scheme 4).

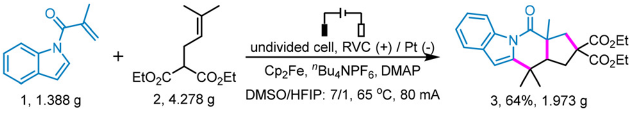


Scheme 2 Scope of *N*-methacryloylindole substrates. Reaction conditions: see Table 1, entry 1, and isolated yield.

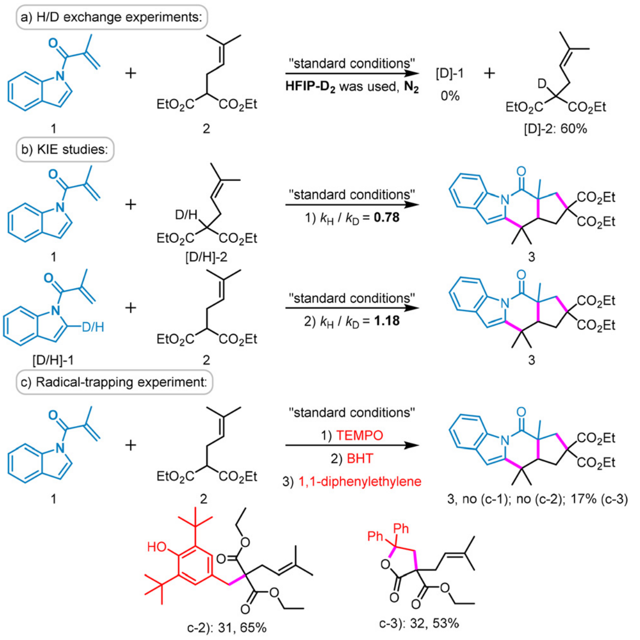


Scheme 3 Scope of naturally derived *N*-methacryloylindole and α-allyl-activated methylene substrates. Reaction conditions: see Table 1, entry 1, and isolated yield.

Given this unique transformation and its potential role in synthetic applications, a series of mechanistic studies were carried out to understand this electrochemical process (Scheme 5 and Fig. 1). A significant H/D exchange of **2** was observed when $[D]_2$-HFIP was used, suggesting a rapid and reversible C–H bond cleavage (Scheme 5a). Moreover, consistent with this finding, a minor kinetic isotope effect (KIE) of $k_H/k_D \approx 0.78$ was obtained (Scheme 5b-**1**). A KIE value 1.18 was also acquired when **2** and [D]-**2** were involved (Scheme 5b-**2**). These results indicated that the C–H bond cleavages in both **1** and **2** might not be the rate-determining step. Furthermore, radical-trapping experiments were investigated, and no product was detected or a dramatic yield reduction was



Scheme 4 Gram-scale synthesis of **3**.



Scheme 5 Key mechanistic findings.

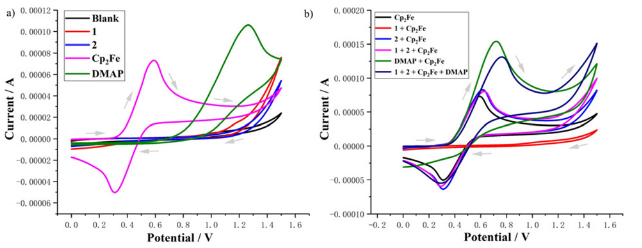
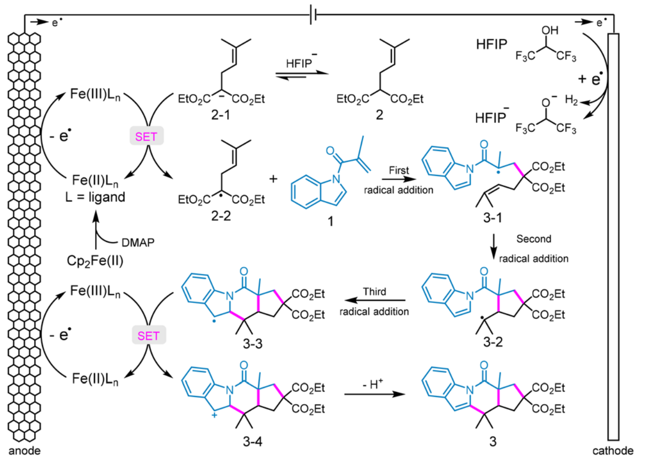


Fig. 1 Cyclic voltammetry experiments, (a) Cyclic voltammetry experiment of sole substrate or additive; (b) Cyclic voltammetry experiment of mixture of Cp_2Fe and other substrate.

observed when radical scavenger TEMPO, BHT or 1,1-diphenylethylene was involved (Scheme 5c). In addition, the corresponding radical-trapping products were generated in 65% and 53% isolated yields in the presence of BHT and 1,1-diphenylethylene, respectively, which strongly supported a radical process occurring for the developed transformation (Scheme 5c-**2** and Scheme 5c-**3**).

Furthermore, cyclic voltammetry experiments were carried out (Fig. 1). It was found that neither substrate **1** nor **2** exhibited any obvious oxidation peak between 0 and 1.5 V (Fig. 1a, red and blue lines). An obvious oxidation peak was observed at 0.59 V or 1.26 V when Cp_2Fe or DMAP was involved (Fig. 1a, pink and green lines). In addition, the inclusion of **1**, **2**, or **1** and **2** showed an oxidation peak comparable to that observed with only Cp_2Fe added (Fig. 1b, black, red, blue, and pink lines).



Scheme 6 Proposed mechanism for the developed electrochemical [3 + 2]/[4 + 2] cyclization.

Interestingly, mixtures of Cp_2Fe and DMAP showed a new oxidation peak at about 0.7 V, which was higher than the oxidation potential of Cp_2Fe and lower than that of DMAP (Fig. 1b, green and brown line). These results indicated that a coordinated Fe(II) species between Cp_2Fe and DMAP was likely generated first, which was then oxidized by the anode to an Fe(III) species, promoting this electrochemical cyclization.

Based on the experimental results and previous reports,[25] a plausible reaction mechanism was proposed (Scheme 6). HFIP was reduced by the cathode to give the corresponding anions with H_2 released, which led to the formation of a carbon-centered anion intermediate **2-1**. Meanwhile, the coordination intermediate Fe(II)Ln (L might be cyclopentadiene and DMAP) was formed and oxidized by the anode to Fe(III)Ln. The carbon-centered radical **2-2** was formed *via* single-electron oxidation of **2-1** by Fe(III)Ln. Radical addition between **2-2** and starting material **1** afforded **3-1**. Afterwards, intramolecular 5-*exo*-trig and 6-*exo*-trig cyclization yielded **3-3**, which was oxidized by Fe(III)Ln or the anode to produce the carbocation intermediate **3-4**. The final product **3** was generated from the aromatization of **3-4**.

Conclusions

In summary, an electrochemically facile transformation of readily available *N*-methacryloylindoles and α-allyl-activated methylenes into corresponding indole-fused polycyclics through [3 + 2]/[4 + 2] cyclization under conditions free of exogenous oxidant was developed. Attributed to the mild and green reaction conditions and the use of Cp_2Fe as a catalyst, which featured lower oxidation potential, an excellent tolerance of diverse functional groups and indole substrates and products was obtained. This electrosynthesis also proved to be efficient for gram-scale synthesis with good water and air compatibility.

Author contributions

C.-K. L. and K. G. designed and guided the experiments. C.-C. Y., L.-F. L. and Y.-Q. Q. conducted the experiments. Z. F. and Z.-F. Z. analyzed the data. C.-K. L. and C.-C. Y. wrote this paper.

Data availability

The data supporting this article, including experimental procedures, full analysis data for compounds and copies of NMR spectra, have been included as part of the ESI.† The crystallographic data for product **19** have been deposited at the CCDC under ID 2422567.†

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This research was supported by Natural Science Foundation of Jiangsu Province, Frontier Project (BK20212003).

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