Flow electroreductive nickel-catalyzed cyclopropanation of alkenes using *gem*-dichloroalkanes

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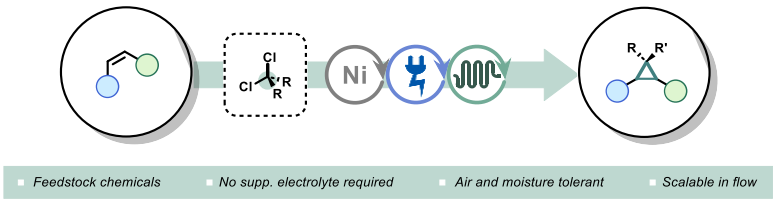
Abstract

Cyclopropanes are valuable motifs in organic synthesis, widely featured in pharmaceuticals and functional materials. Herein, we report an efficient electrochemical methodology for the cyclopropanation of alkenes, leveraging a nickel-catalyzed process in continuous-flow. The developed protocol demonstrates broad substrate scope, accommodating both electron-rich and electron-poor alkenes with high functional group tolerance. Beyond dichloromethane as a feedstock methylene source, the methodology enables the synthesis of methylated, deuterated, and chloro-substituted cyclopropanes. Mechanistic investigations suggest the electro-generation of a nickel carbene as key intermediate. Notably, the reaction operates under ambient conditions, tolerates air and moisture, and achieves scalability through continuous-flow technology, offering a straightforward route to multi-gram quantities with enhanced throughput.

Graphical abstract



Keywords: Electrocatalysis • Flow chemistry • cyclopropanation • dichloromethane • electrochemistry

Introduction

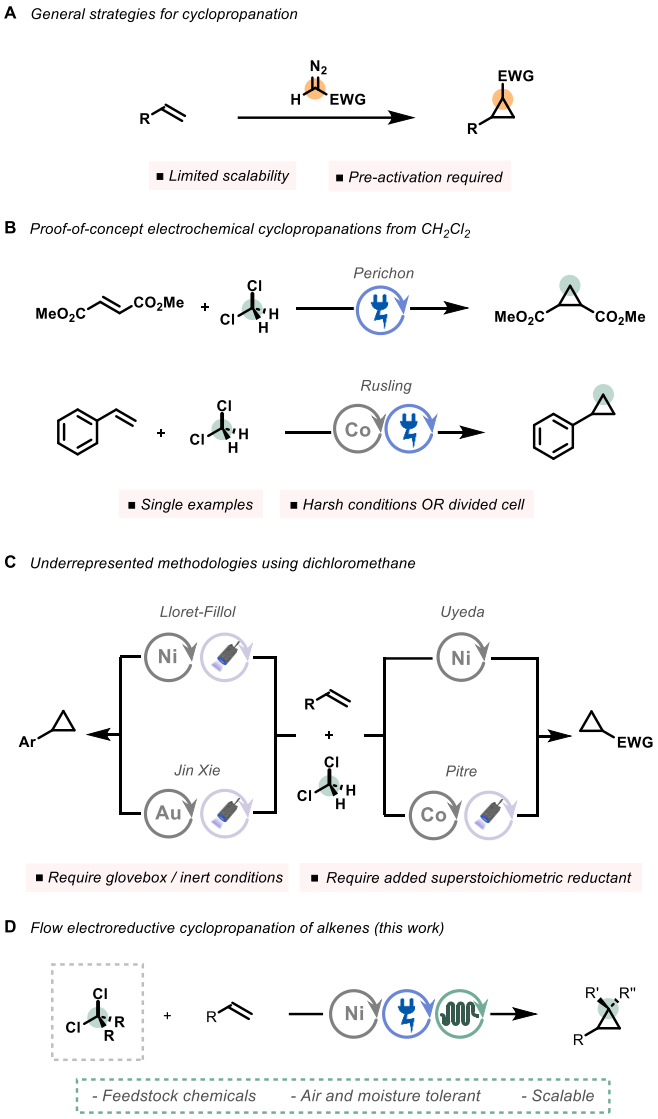
The cyclopropane ring is a key motif in organic chemistry, often employed as an isostere for alkyl, arene, and alkene groups.[1] This strained three-membered carbocycle is a structural feature in numerous drugs and fragrances, and serves as a versatile building block for complex molecule synthesis.[2] Consequently, the seamless integration of cyclopropanes into complex molecular frameworks is a significant goal within the synthetic organic chemistry community. Since the seminal development of the Simmons-Smith and Corey-Chaykovsky reactions,[3] diazo-based carbene transfer reactions have subsequently emerged as the dominant strategy for converting alkenes into cyclopropanes (**Scheme 1A**).[4] Despite their utility, the inherent risks associated with diazo compounds — such as rapid exothermic heat release and gas evolution — have hindered their application in large-scale industrial processes.[5] Alternative approaches employing radical or redox-based methodologies have emerged as valuable complements, yet they often require additional steps to prepare methylene transfer reagents, which limits their practicality.[6] Consequently, the development of scalable and practical methods to synthesize cyclopropanes from readily available feedstock chemicals remains a key challenge.

Dichloromethane, an abundant and inexpensive methylene source, was first utilized in an electroreductive cyclopropanation by Perichon and co-workers in 1990.[7] This study established proof of concept for the transformation of electron-deficient alkenes, albeit under harsh conditions due to the inert nature of the C–Cl bond. In 2001, Rusling and co-workers achieved a milder Vitamin B_{12}-mediated electroreduction of dichloromethane in a divided cell setup, demonstrating improved Faradaic efficiency. However, this method remained limited to the cyclopropanation of styrene (**Scheme 1B**).[8] Building on earlier work involving nickel carbene formation from dibromomethane with zinc as a reductant,[9] Nédélec and co-workers demonstrated an electroreductive activation of a nickel complex capable of cyclopropanating methyl maleates.[10] Despite these advances, the synthetic potential of electroreductive cyclopropanation remains underexplored, with opportunities to further expand its scope and efficiency. Additionally, the need for more accessible and standardized electrochemical setups presents an avenue for future optimization and broader applicability in synthetic laboratories.

To date, a handful of recent studies have explored the use of dichloromethane as a C1 precursor for cyclopropanation (**Scheme 1C**). Xie and co-workers employed dinuclear gold catalysts to activate dichloroalkenes for cyclopropanation and annulation reactions.[11] Uyeda and co-workers showcased a reductive cyclopropanation utilizing a Ni-PyBOX catalyst, representing another significant advancement.[12] Pitre and co-workers extended Rusling's foundational work by developing a Vitamin B_{12}-photocatalytic cyclopropanation of Michael acceptors using CH_2Cl_2.[13] Most recently, Lloret Fillol and co-workers reported a photoredox-mediated nickel-catalyzed cyclopropanation of alkenes.[14] While these approaches demonstrate innovative strategies, the reliance on superstoichiometric metal reductants or stringent anaerobic glovebox conditions presents challenges to scalability and practicality.

We envisioned that electrochemistry could offer a solution to these limitations by eliminating the need for additional chemical reductants while enabling the selective transformation of diverse and complex organic substrates.[15] Furthermore, flow chemistry has recently emerged as a transformative technology in electrosynthesis.[16] By utilizing a standardized electrochemical flow cell, we anticipated addressing challenges such as ohmic drop, mass transfer limitations, scalability, and procedural robustness.[17] Despite these technological advances and the promising foundations laid by

early electrochemical studies, electrochemical cyclopropanation remains surprisingly underexplored in the literature.[18] Leveraging the electrochemical flow cell developed in our laboratory,[19] we report herein the development of a flow electroreductive nickel-catalyzed protocol that enables a mild, broadly applicable and scalable cyclopropanation of alkenes using bulk chemical dichloromethane and other widely available *gem*-dichloroalkanes as methylene precursors (**Scheme 1D**).

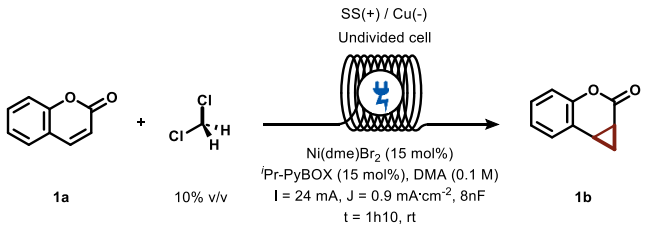


Scheme 1. A. General cyclopropanation strategy. **B.** Electrochemical proof-of-concept for cyclopropanation from CH_2Cl_2. **C.** Underrepresented methodologies using dichloromethane. **D.** Flow electroreductive cyclopropanation from CR_2Cl_2.

We began our investigation by selecting coumarin (**1a**) as a model substrate for optimization studies. Initially, electrochemical cyclopropanation of **1a** was carried out in an undivided batch electrochemical cell using a Ni-PyBOX complex, achieving a 67% yield of **1b** (**Table S1**). Encouragingly, thorough optimization allowed us to rapidly adapt the reaction conditions to a continuous-flow setup (**Table S2-S11**). This transition eliminated the need for an inert atmosphere, enhancing the practicality of the protocol. Additionally, the improved mass transfer in the flow cell significantly increased the throughput, from 13 μmol·h^{-1} in batch to 112 μmol·h^{-1} in flow (**Table 1, entry 1**). The reduced inter-electrode distance in the electrochemical flow cell also enabled us to omit the supporting electrolyte without compromising the yield (**Table 1, entry 2**). Control experiments confirmed the electrochemical nature of the reaction, as no product was obtained in the absence of an electrical current, with only the starting material recovered (**Table 1, entry 3**). However, reducing the catalyst loading led to a decrease in yield to 50% (**Table 1, entry 4**). Similarly, decreasing the

residence time, and thus reducing the total number of electrons exchanged, lowered the yield of **1b** (**Table 1, entry 5**). An extensive ligand screening identified ^{i}Pr-PyBOX as a cost-effective and optimal ligand for the reaction (**Table 1, entry 6, Table S3**).[20] Increasing the volumetric proportion of dichloromethane resulted in a slight decrease in product formation (**Table 1, entry 7**). Altering the sacrificial anode and cathode materials did not improve the yield of **1b** (**Table 1, entries 8-9, Tables S7-8**). Notably, when the optimized flow conditions were applied to a batch setup, significant degradation of the starting material occurred, resulting in a yield of only 8% for **1b** (**Table 1, entry 10**). This highlights the advantages of the continuous-flow setup for our cyclopropanation conditions.

Table 1. Optimization of reaction conditions.[a]

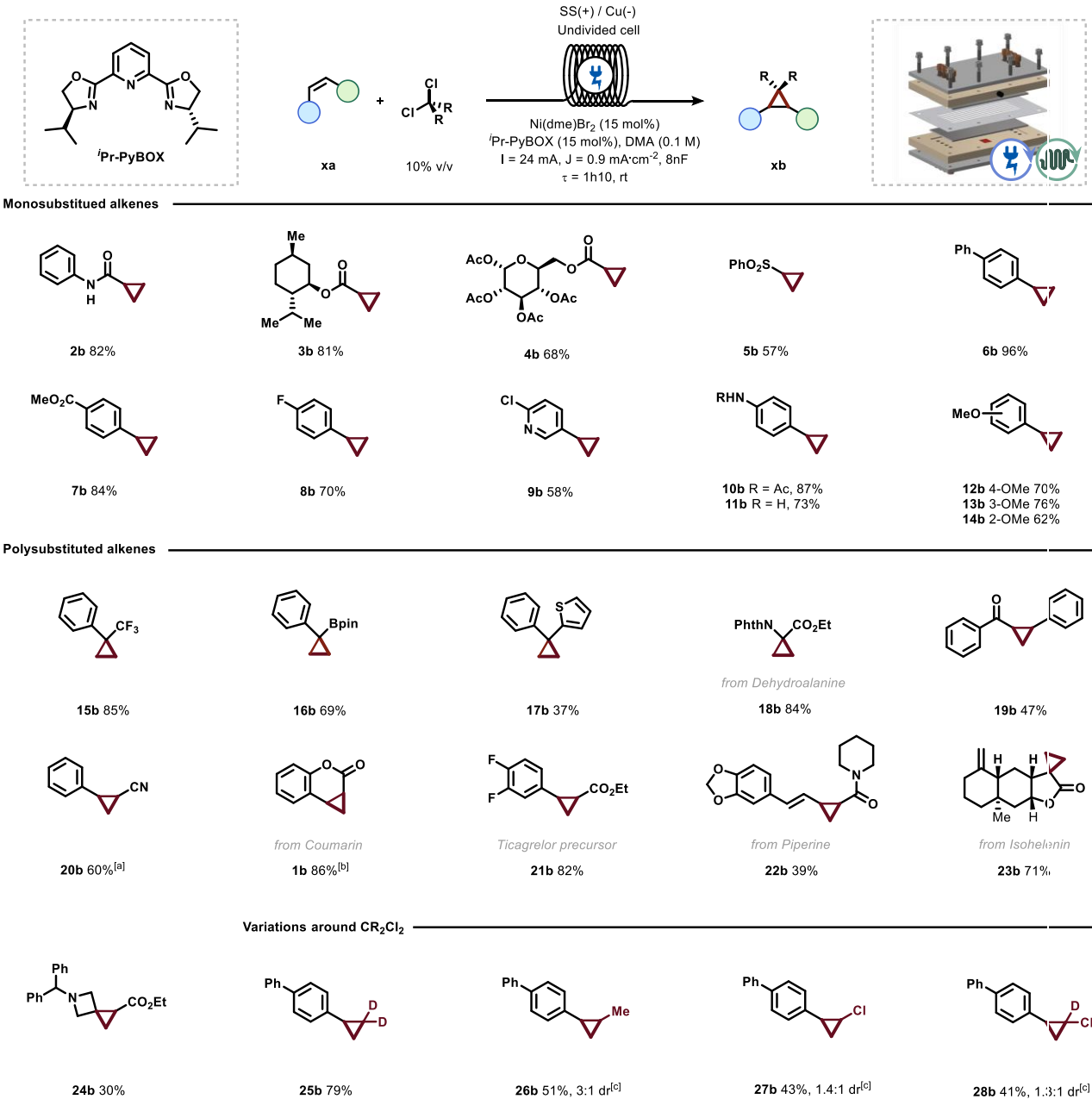


Entry	Variation from optimal conditions	Yield (%)[b]
1	None	87 (84[c])
2	With nBu$_4$NBF$_4$ (1 equiv)	85
3	no current	0
4	5 mol% Ni(dme)Br$_2$ and ^{i}Pr-PyBOX	50
5	4nF, τ = 35 min	64
6	20% v/v dichloromethane	70
7	Bn- and H- instead of ^{i}Pr-PyBOX	6, 61
8	Zn(+) instead of SS(+)	42
9	Gr. (-) instead of Cu(-)	82
10	Batch, 0.9 mA·cm^{-2}, 8nF, 42.8 h	8[c]

[a] Standard conditions: reaction performed on a 30 µmol scale (see Supplementary Information for experimental details). [b] Yields determined by NMR analysis of the crude reaction mixture using 1-3-5-trimethoxybenzene as an external standard. Values in parentheses are yields of the isolated compound. [c] Reaction performed on 0.2 mmol scale.

Next, we explored the scope of alkenes that could undergo cyclopropanation using our electrochemical protocol, focusing first on the effects of steric hindrance and electronic properties of the double bond (**Scheme 2**). Using CH_2Cl_2 as the methylene source, we found that monosubstituted alkenes readily participated in the transformation. Michael acceptors, including acrylamides (**2b**), acrylates (**3b,4b**) and phenyl vinyl sulfones (**5b**), afforded cyclopropanation products in good to excellent yields. These results align with the hypothesis of a nucleophilic nickel carbene acting as the methylene transfer agent.[12] Electron-poor aromatic alkenes also proved compatible with our reaction conditions (**6-9b**), with substrates containing halides and pyridine moieties (**8b, 9b**) delivering the desired products efficiently. Notably, unlike previous methods, our protocol also tolerated electron-rich aromatic alkenes, which yielded high product conversions under optimized flow conditions (**10-14b**). The method's compatibility with protic functional groups, such as amides (**2b**, **10b**) and aniline

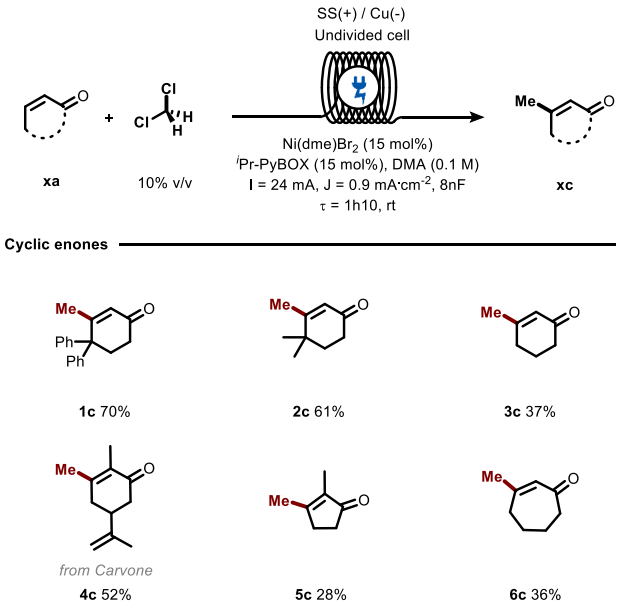
(**11b**) , is particularly noteworthy, as these groups typically quench ylide intermediates in Corey-Chaykovsky cyclopropanation reactions due to their acidity. Electron-poor 1,1-disubstituted alkenes were also suitable under our conditions (**15-18b**). Substrates bearing trifluoromethyl (**15b**) and thiophene (**17b**) moieties were well tolerated, producing cyclopropanes in synthetically useful yields. The tolerance towards pinacol borane ester groups (**16b**) is especially significant, as it enables further functionalization through Suzuki-Miyaura-type cross-coupling reactions. Dehydroalanine (**18b**) reacted smoothly, delivering the corresponding unnatural amino acid in excellent yield. A series of 1,2-disubstituted alkenes with electron-withdrawing groups, such as chalcone (**19b**), cinnamonitrile (**20b**), and coumarin (**1**), were efficiently converted to their respective cyclopropane derivatives. Our protocol also accommodated structurally complex and biologically relevant substrates, including the ticagrelor precursor (**21b**), piperine (**22b**), and isohelenin (**23b**). Additionally, a trisubstituted alkene derived from azetidine demonstrated reactivity under our conditions, producing the corresponding biologically relevant spiro-compound **24b**.[21] This result highlights the method's ability to tolerate sterically hindered alkenes, further broadening its applicability.



Scheme 2. Scope of the flow electroreductive nickel-catalyzed cyclopropanation of alkenes. Reactions performed on 0.2 mmol scale. All yields are those of isolated products (see Supplementary Information for experimental details). [a] Two reactors in series were used. [b] I = 36 mA, J = 1.4 mA.cm^{-2} was applied. [c] I = 48 mA, J = 1.8 mA.cm^{-2} was applied.

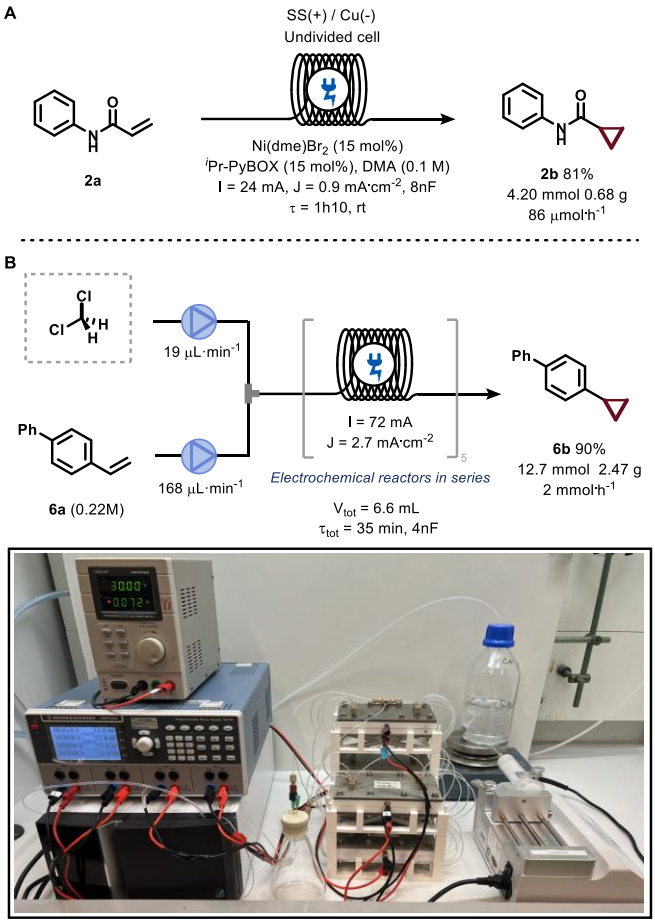
We then explored the use of a diverse set of commercially available *gem*-dichloroalkanes as carbene precursors in our reaction protocol, using 4-phenylstyrene as the coupling partner (Scheme 2). Deuterated dichloromethane was successfully employed, leading to the formation of the corresponding deuterated cyclopropane product (**25b**). Similarly, 1,1-dichloroethane was activated under the reaction conditions to afford the cyclopropane derivative (**26b**) in good isolated yield. Furthermore, the use of chloroform and deuterated chloroform provided products **27b** and **28b**, respectively, demonstrating the regioselective installation of a carbon-chlorine bond within the cyclopropane ring.

Interestingly, when cyclic enones were subjected to the reaction conditions, the corresponding β-methylated products were obtained instead of the anticipated cyclopropanes (**Scheme 3**). A variety of six-membered cyclic enones (**1-4c**), as well as five- and seven-membered variants (**5-6c**), were successfully methylated using this unprecedented electrochemical strategy. Investigation into this unexpected selectivity revealed that the strained structure of the cyclic substrates was a key factor, as linear enones did not yield the β-methylated products (**19b**). Control experiments further confirmed that the β-methylated products were not formed via degradation of the cyclopropane ring (**Scheme S9**). Notably, similar β-alkylation has been reported in cyclopropanation reactions and is often attributed to a carbene-mediated C─H insertion at the β-position of enones.[22] Further studies are ongoing to fully elucidate the mechanistic factors driving this selectivity. The formation of β-methylated enones is particularly noteworthy, as, to the best of our knowledge, only two precedents for such a transformation in a single-step procedure exist in the literature, which would otherwise require a Saegusa-Ito-type reaction sequence.[23]



Scheme 3. Scope of the flow electroreductive nickel-catalyzed methylation of cyclic enones. Reactions performed on 0.2 mmol scale. All yields are those of isolated products (see Supplementary Information for experimental details).

To further showcase the synthetic potential of our method, we investigated the scalability of our continuous-flow procedure (**Scheme 4**). It is worth noting that during the scope investigation, we observed that the stainless-steel sacrificial anode could be reused over 50 times without noticeable degradation in electrode performance (**Table S17**). Leveraging this robustness, a scale-up experiment was conducted to produce over 4 mmol of **2b** during a 49-hour uninterrupted run, achieving an isolated yield nearly identical to that obtained on a 0.2 mmol scale. This indicates that anode surface degradation and potential cathode passivation over extended operation times remain minimal (**Scheme 4A**). Additionally, after a brief re-optimization of the protocol for the cyclopropanation of **6b** (**Table S18**), we enhanced throughput per reactor from 112 to 448 μmol·h^{-1} by connecting five electrochemical flow reactors in series. This setup enabled the isolation of 2.47 g of **2b** without significant yield loss, highlighting the advantages of continuous-flow technology for scaling up electrochemical processes (**Scheme 4B**).



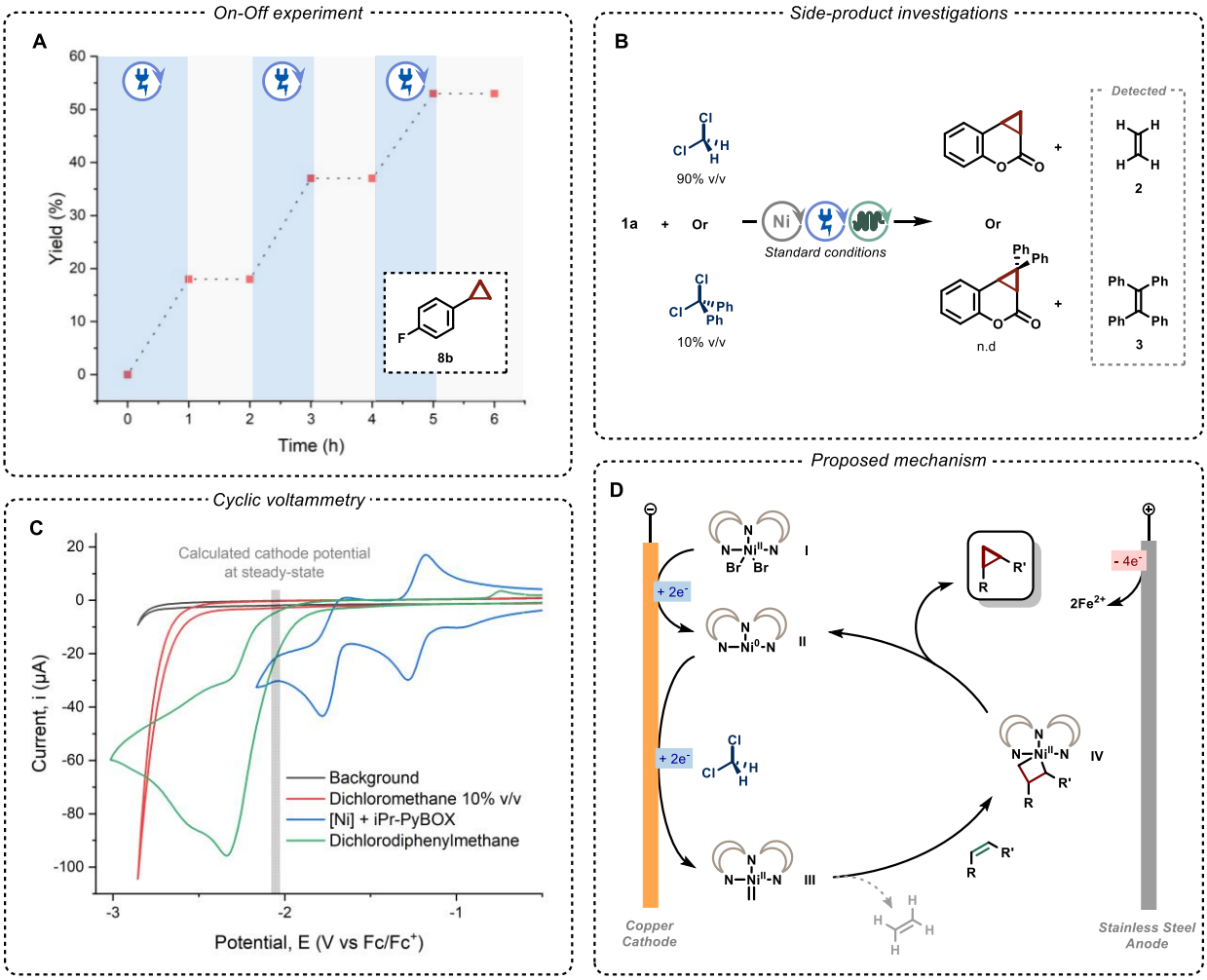
Scheme 4. Scaling up the electroreductive nickel-catalyzed cyclopropanation of alkenes. **A.** Productivity assessment of the reactor over 49 hours. **B.** Multi-gram scale electroreductive cyclopropanation in continuous flow with 5 reactors in series.

Having established the scope, limitations, and scalability of our electrochemical cyclopropanation methodology, we sought to investigate its key mechanistic steps (**Scheme 5**). Continuous electrolysis was confirmed as essential for the reaction by conducting on-off cycles during the cyclopropanation of **8b**. The resulting plot demonstrated that the catalytic cycle's active species must be electrochemically regenerated to sustain the process (**Scheme 5A**).

Reversing the proportions of dichloromethane to DMA resulted in gas formation, observed as a gas-liquid segmented flow emerging from the reactor.[24] Gas chromatography analysis identified the gas as ethylene (**Figures S9**). Previous studies by Kanai, Nédélec, and Uyeda proposed the formation of a nickel carbenoid under reductive conditions with suitable methylene precursors.[9-10, 12] Similarly, Schrock and Gladysz observed ethylene gas evolution while studying rhenium and tantalum carbenes, attributing this to the homocoupling of two metal carbenes.[25] Chen and co-workers also reported ethylene formation, indirectly detected via *in-situ* polyethylene generation, when using ammonium triflates as a methylene source to form nickel carbenes.[26] However, it is also known that direct electrochemical reduction of dichloromethane can yield ethylene, although methane is typically the major product.[27] To determine whether ethylene formation in our system was associated with nickel carbenes, control experiments confirmed the absence of methane in the collected samples (**Figure S10**). These results suggest that ethylene evolution in our reaction is consistent with the formation of a nickel carbene as a key intermediate (**Scheme 5B**). Further evidence for this pathway was obtained when dichlorodiphenylmethane failed to form the desired cyclopropane due to reactor clogging. Analysis of the solid product revealed tetraphenylethylene, indicative of homocoupling between nickel carbenes (**Scheme 5B**).

To gain deeper insight into the mechanism, cyclic voltammetry (CV) experiments were conducted. The Ni-^{i}Pr-PyBOX complex exhibited a redox couple at -1.23 V vs. Fc/Fc^{+}, corresponding to the $[Ni^{II}]/[Ni^{I}]$ transition, followed by an irreversible cathodic peak at -1.78 V vs. Fc/Fc^{+}, which can be attributed to the $[Ni^{I}]/[Ni^{0}]$ transition (**Scheme 5C**).[28] Dichloromethane itself displayed no significant cathodic peaks until analyzed under reaction conditions (10% v/v). In this setting, the solvent wall shifted with an onset potential of -2.48 V vs. Fc/Fc^{+}, likely corresponding to the direct reduction of CH_2Cl_2. Under steady-state reaction conditions, the flow cell's potential was measured at 1.02 V, with iron oxidation occurring at -1.07 V vs. Fc/Fc^{+}.[29] This implies a cathodic potential of approximately -2.09 V vs. Fc/Fc^{+} (**grey area, Scheme 5C**). Taken together, these observations support a nickel-mediated activation of dichloromethane as the primary pathway for cyclopropanation. When analyzing the CV of diphenyldichloromethane, an irreversible cathodic peak appeared at -2.34 V vs. Fc/Fc^{+}, further supporting the hypothesis that the corresponding homocoupling product is formed predominantly through nickel-mediated activation.

Based on these results, we propose a plausible mechanism for the Ni-electrocatalytic cyclopropanation (**Scheme 5D**). The characterization of by-products and insights from cyclic voltammetry strongly indicate a nickel-mediated activation of dichloromethane. The catalytic cycle likely begins with the reduction of $NiBr_2$-^{i}Pr-PyBOX (**I**) at the cathode, generating Ni^{0}-^{i}Pr-PyBOX (**II**). Further reduction of **II** in the presence of dichloromethane facilitates the formation of a nickel carbene intermediate (**III**), which can either undergo homocoupling or proceed toward cyclopropanation. The cyclopropanation pathway involves the cycloaddition of **III** with the alkene substrate, forming a nickelacyclobutane intermediate (**IV**).[12] Reductive elimination from **IV** then produces the desired cyclopropane product, regenerating **II** and completing the catalytic cycle.



Scheme 5. Mechanistic investigation and proposed mechanism. **A.** On-off experiment. Data obtained by q ^{19}FNMR experiments using 1-fluoronaphtalene as internal standard. **B.** Investigation of side-product formation. **2** was detected with GC-FID. **3** was detected with HRMS. **C.** Cyclic voltammetry experiments. The baseline is a solution of 0.1 M *n*Bu$_4$BF$_4$ in dry DMA. 3 mM analyte concentration is used unless otherwise stated. **D.** Proposed mechanism.

In conclusion, we have developed an efficient and practical electrochemical cyclopropanation method in continuous-flow. The substrate scope encompasses a wide range of electron-poor and electron-rich alkenes, demonstrating high functional group tolerance. Moreover, the methodology extends beyond simple dichloromethane to enable the synthesis of methylated, deuterated, and chloro-substituted cyclopropanes. Our findings strongly support that this novel cyclopropanation process operates via the reductive in-situ generation of nickel carbenes. We believe this method represents an advancement for the rapid synthesis of high-value cyclopropanes, as it can be performed under ambient conditions, including in the presence of air and moisture. Furthermore, its compatibility with continuous-flow technology enables scalability to multi-gram scales, offering enhanced throughput compared to existing protocols using dichloromethane as a methylene source. Ongoing investigations in our laboratory aim to further elucidate the factors governing the selectivity between cyclopropanation and methylation and to develop a detailed mechanistic rationale for this catalytic divergence.

Supporting information

The authors have cited additional references within the Supporting Information.[6a, 9, 12-14, 18h, 19a, 27-30]

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