Strain-Released Hydrogenation of Donor-Acceptor Cyclopropane and Cyclobutane via Electrochemical Site Selective Carbonyl Reduction

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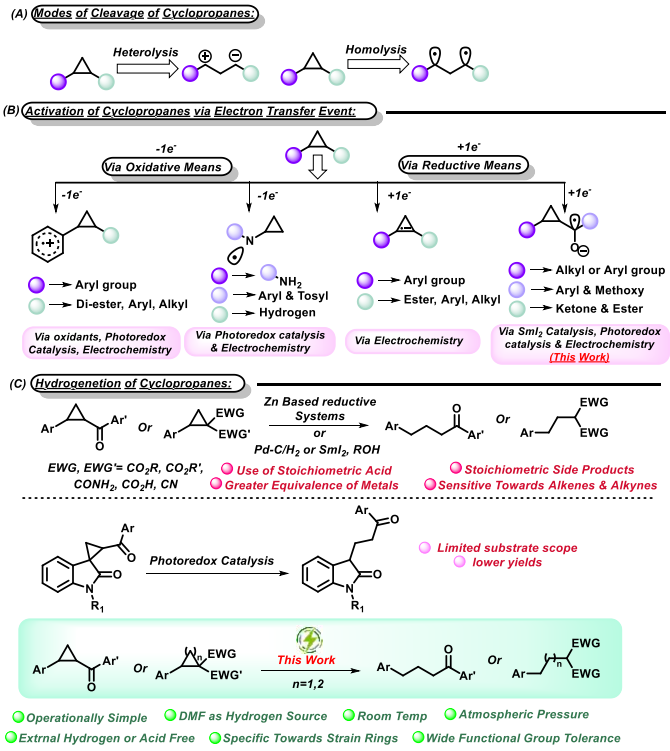
Abstract: An external oxidant or reductant, acid-free electrochemical protocol is established towards the hydrogenation of strained rings at room temperature and atmospheric pressure. After control experiments, it is revealed that the reaction is initiated via the reduction of the carbonyl group. The methodology is highly specific towards the strained rings and has a broad functional group tolerance.

The pioneering journey of ring-opening reactions of cyclopropane was started long back in the 1970s.[1, 2] The ring strain of 115 KJmol^{-1} with inefficient orbital overlap induces π- character in bent C-C bonds of cyclopropanes.[3] Owing to the Pitzer strain and Prelog strain[4, 5] cyclopropanes are widely used as a precursor for the synthesis of various carbocycles, heterocycles, macromolecules, and other ring-opening reactions like cycloadditions,[6-8] rearrangements,[9, 10] bifunctionalization[11, 12]. Two modes of strain release are known for the cyclopropanes- (a) heterolysis to generate zwitterionic species and (b) homolysis to generate radical intermediates. The traditional methods for the activation of cyclopropanes involved thermolysis, transition metal catalysis, Lewis,[13-15] and Bronsted acid catalysis[16, 17], organocatalysis[18, 19] which led to the generation of zwitterionic intermediate [Scheme 1(A)]. Another major pathway that involves the activation of cyclopropane involves the electron transfer reaction. Electron transfer can again be classified into two broad categories- (a) electron transfer from the cyclopropanes (via oxidative means),[20-22] and (b) electron transfer to the cyclopropanes (via reductive means).[23] Certain donor and acceptor groups are incorporated to enhance the reactivity of cyclopropane. Now, the donor groups are generally electron-rich, and the acceptor groups are electrophilic. From the perspective of electron transfer reaction, donor or electron-rich moieties are susceptible towards oxidation, and electron-accepting groups are prone towards reduction. Electron transfer can broadly be categorized into two pathways (a) outer sphere electron transfer (the participating redox centers are not linked via covalent bonds during electron transfer).[24] (b) inner sphere electron transfer (the participating redox centers are linked via covalent bonds).[24] Various metal-mediated processes, organic oxidant or reductant-mediated reactions, photo redox catalysis, and electrochemical reactions are the basis of electron transfer reactions or redox reactions. There are several reports of the activation of cyclopropanes via electron transfer processes.[25-28] The Aryl group acts as a donor group both in the case of aryl cyclopropanes and donor-acceptor cyclopropanes (DACs).



Scheme 1. Mode of activation of cyclopropane.

One of the popular strategies for the activation of such cyclopropanes are oxidation of the aryl group to generate radical cation intermediates [Scheme 1(B)][27] via oxidant-mediated processes, visible light photo redox catalysis, and electro-organic chemistry. *N-aryl* or *N*-tosyl groups also acted as popular donor groups which are prone towards oxidation.[29, 30] Here, oxidation leads to the generation of *N*-centre radical or radical cation intermediates over the nitrogen center. Due to the possession of π character in the C-C bond of strained rings, activation of the cyclopropane ring can also be done directly via one-electron transfer to generate radical anion intermediates electrochemically.[31] Another reductive pathway for the activation of cyclopropane is the reduction of the carbonyl group adjacent to the cyclopropane. There are several methodologies known like SmI_2 and photoredox catalysed single electron transfer for the reduction of carbonyl compounds to generate the radical anion

intermediate, which subsequently leads to the homolysis of the cyclopropane ring.[23, 26, 32]

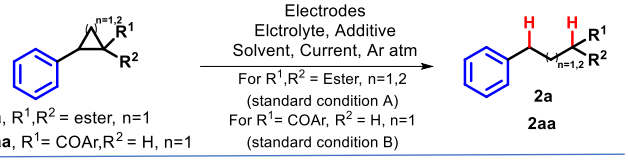
Our lab has been working in the field of strain rings for a long and in the last few years, we have discovered a few electro-oxidative protocols for the activation of cyclopropanes. Ring-opening hydrogenation for DACs is known via the use of Pd-C/H_2,[33, 34] SmI_2-ROH,[35, 36] and Zn-AcOH-based systems[37] [Scheme 1(C)]. Such methodologies used harsh reaction conditions, which resulted in the over-reduction or hydrogenation at the multiple bonds. Recently, photoredox catalyzed hydrogenation of donor acceptor cyclopropanes are reported, but substrate scope is limited.[38] Herein, we are reporting the ring-opening hydrogenation of DACs and cyclobutanes via carbonyl reduction using DMF as a hydrogen source. The protocol is highly selective for the strained rings and avoids the usage of external acid or hydrogen sources.

To test our hypothesis, we initially took dimethyl 2-phenylcyclopropane-1,1-dicarboxylate (**1a**) as a model substrate, Bu_4NPF_6 (1 equiv.) as a supporting electrolyte, DMF as a solvent, aluminum as anode and carbon as cathode. The electrolysis is performed at a constant current of 10 mA, albeit no product formation is observed (Table 1, entry 2A). Screening of electrodes, like changing the anode material from Al(+) to Mg(+), leads to the generation of our desired product with a 32% yield (Table-1, entry 3A). Solvents like CH_3CN are employed, which resulted in the formation of the desired product (**2a**) in 37% yield (Table-1, entry 4A). Other solvents DMSO, DMA, MeOH failed to give the desired product **2a** (Table 1, entry 5A). Several variations in the electrolytes, like Bu_4NBr, Bu_4NI provide the desired product **2a** in 30% yield (Table-1, entry 6A). When the reaction is performed in the presence of the additive Bu_4NOAc taking 2 equiv. of Bu_4NPF_6 as an electrolyte resulted in the formation of the desired product **2a** in 40% yield (Table-1, entry 7A). Using 2 equiv. Bu_4NOAc as an electrolyte provides **2a** in 46% of yield (Table-1, entry 8A). Finally, by using 1 equiv. of Bu_4NPF_6 as a supporting electrolyte and 1 equiv. of activated Bu_4NOAc in Sn as an anode and carbon as a cathode under an argon atmosphere give the desired product **2a** in 90% yield (Table-1, entry 1A).

Furthermore, we subjected the cyclopropyl ketone **1aa** to the standard condition A. However, a moderate yield was obtained (Table 1, Entry 2B). Changing the electrolyte to Bu_4NClO_4 provided the desired product with a 52% yield (Table 1, Entry 3B). Further changing the anode from Sn (+) to Zn (+) led to the formation of the product in 59% (Table 1, Entry 4B). After that, an array of cathode materials is verified, among which Sn (-) provided the best result (Table 1, Entry 1B).

With the optimized condition in hand, we subsequently explored the scope of donor-acceptor cyclopropanes towards the formation of 1,3 hydrogenated products. Firstly electron-donating groups like an isopropyl group at the *para* position or a methoxy group at the *ortho* position tolerated well to provide the desired product in good to excellent yields **(2b,** 73%**; 2c,** 90%**)**. Changing the position of the methoxy group to the para position and altering the ester part at the same time provided the product **(2d,** 70%**)** with good yields. Introducing an electron-withdrawing group like trifluoromethyl at the *meta*-position along with a methoxy group led to the generation of the desired product in good yields **(2e,** 62%**)**. Changing the aryl group to the phenyl [1,3] dioxole group

Table 1. Reaction Optimization.



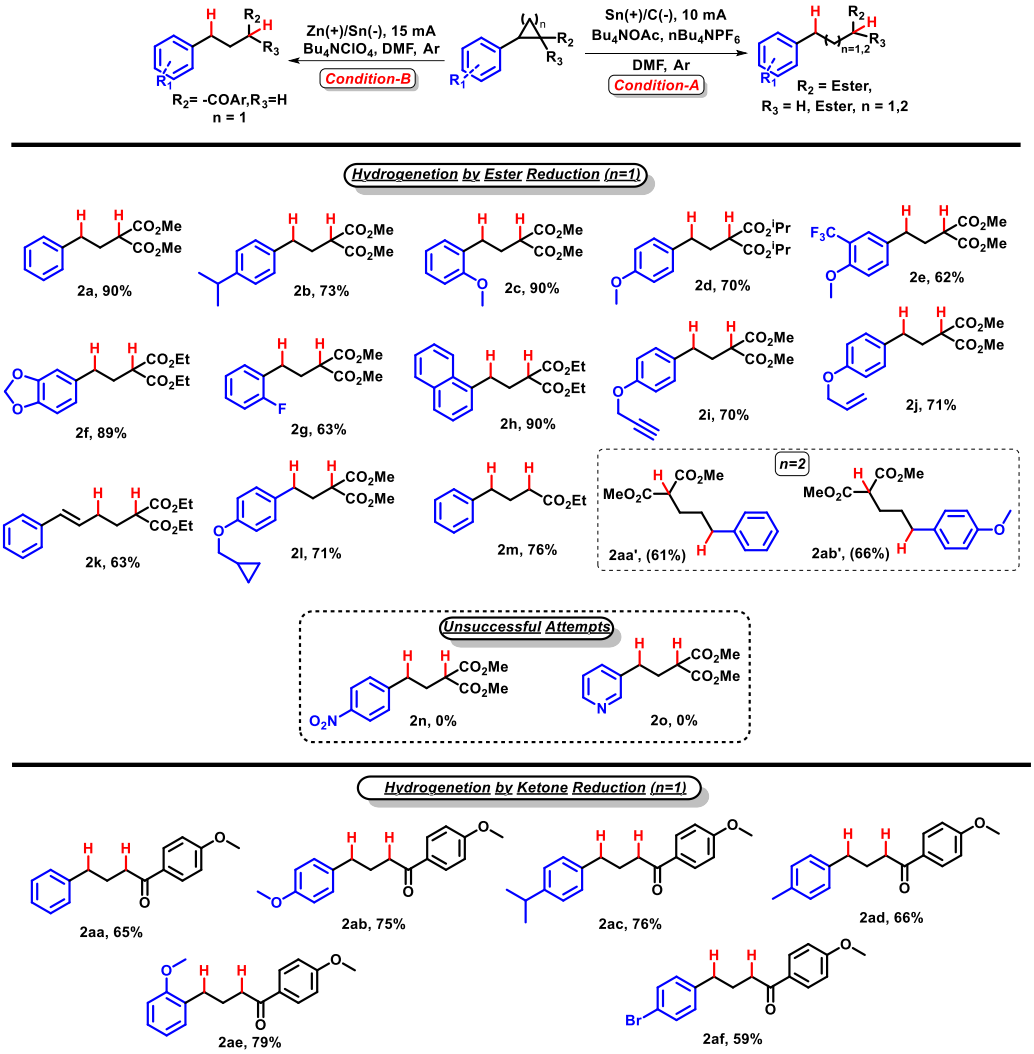
1a, R^1,R^2 = ester, n=1
1aa, R^1= COAr,R^2 = H, n=1

2a
2aa

Entry No.	[a]Deviation From the Standard Condition A	Yield (%)[c]
1A	None	90
2A	Al(+) instead of Sn(+)	0
3A	Mg(+) instead of Sn(+)	32
4A	CH_3CN instead of DMF	37
5A	DMSO, DMA, MeOH instead of DMF	0
6A	Bu_4NBr and Bu_4NI as electrolyte	30
7A	Absence of additive	40
8A	Bu_4NOAc as electrolyte	46
	[b]Deviation From the Standard Conditions B	
1B	None	65
2B	Bu_4NPF_6 as an electrolyte, Bu_4NOAc as an additive, Sn(+) as anode, Carbon as cathode	45
3B	Bu_4NClO_4 as a supporting electrolyte	52
4B	Zn (+) as anode	59

Standard Reaction Condition: [a]Condition A: **1a** (0.192 mmol), Electrolyte Bu_4NPF_6 (1 equiv., 0.192 mmol), additive Bu_4NOAc (1 equiv., 0.192 mmol) (activated for 24 hrs before using), Tin as anode and carbon as cathode. DMF as solvent (3 mL), Reaction performed at 10 mA constant current in room temperature for 4-10 h. [b]Condition B: **1aa** (0.192 mmol), electrolyte Bu_4NClO_4 (2 equiv., 0.384 mmol), DMF as solvent (3 mL), Zn as anode, Sn as cathode. Reaction performed at 15 mA constant current in room temperature for 2 h. [c]Yields (%) are expressed as isolated yields.

deduced the product in excellent yields **(2f,** 89%**)**. Fluorine at the ortho position resulted in the formation of **2g** in 63% yield. Incorporating naphthyl as a donor part deduced the product **2h** in excellent yields. Thereafter, to validate the efficacy and specificity of our designed methodology, sensitive groups that are prone towards hydrogenation are also checked. Incorporating a terminal triple bond **(2i)** or a terminal double bond **(2j)** tolerated well towards our designed methodology to generate products with good yields. Motivated by our affirmative success the methodology is also subjected to an internal double bond vicinal. Motivated by our affirmative success the methodology is also subjected to an internal double bond vicinal to the strained ring and product **2k** obtained good yields. Gratifyingly a terminal strained ring also afforded product **2l** in good yields. Changing



Scheme 1. Substrate scope.

the acceptor part to a monoester formed the desired product **2m** in good yields. The methodology is successfully extended towards donor-acceptor cyclobutane diester to generate the hydrogenated products **2aa', and 2ab'** in good yields. Strongly electron withdrawing groups like nitro at the *para* to the phenyl ring (**2n**) failed to provide the desired product, probably due to the lower reduction potential of the para-substituted nitro benzene than the ester part. Similarly, changing the donor part to a pyridine moiety (**2o**) also proved detrimental to our designed methodology because of the lower reduction potential of the pyridine rather than the ester motif. Further, we have extended our methodology towards the cyclopropyl ketones (**2aa-2af**). Firstly, variation with respect to donor part is performed. Electron donating groups like methoxy, isopropyl, and methyl at the *para* position of the phenyl ring tolerated well to provide the desired product (**2ab, 2ac, 2ad**) in good yields. Changing the methoxy group to the *ortho* position led to the generation of the product (**2ae**) in excellent yields. A bromo group at the *para* of the donor ring provided the desired product in moderate yields (**2af**).

To elucidate the mechanism of our designed methodology a series of experiments are performed. Initially, the reaction is performed in the standard condition in the absence of electricity [Fig 2. (1)-(A)] but no desired product is formed. This proved the paramount role of electricity in the reaction. To have a clear insight into the reaction initiation pathway, we have subjected aryl cyclopropane (**1a"**) to our standard reaction condition [Fig 2. (1)-(B)], but no desired product is detected. Such a result depicted the role of the ester group in the initiation of the reaction. The reaction is plausibly initiated via the carbonyl reduction pathway, which is further clarified in the CV section. Moreover, it is observed that in the absence of the additive Bu_4NOAc the yield of **2a** decreased to 29% [Fig 2. (1)-(C)]. This signifies the role of Bu_4NOAc as an additive. Furthermore, to find out the source of hydrogen in the reaction medium we have performed the reaction in the presence of activated molecular sieves and freshly prepared anhydrous DMF but in the absence of the additive Bu_4NOAc [Fig 2. (1)-(D)], no desired product is detected. At this stage, we hypothesized that DMF might be the source of hydrogen in the electrochemical reaction. Since DMF contained trapped water, we further performed a water sensitivity experiment [Fig 2. (2)]. We have taken the NMR yield of the product in different time intervals in standard conditions. After that 2 equiv. of water is added in different time intervals, and the

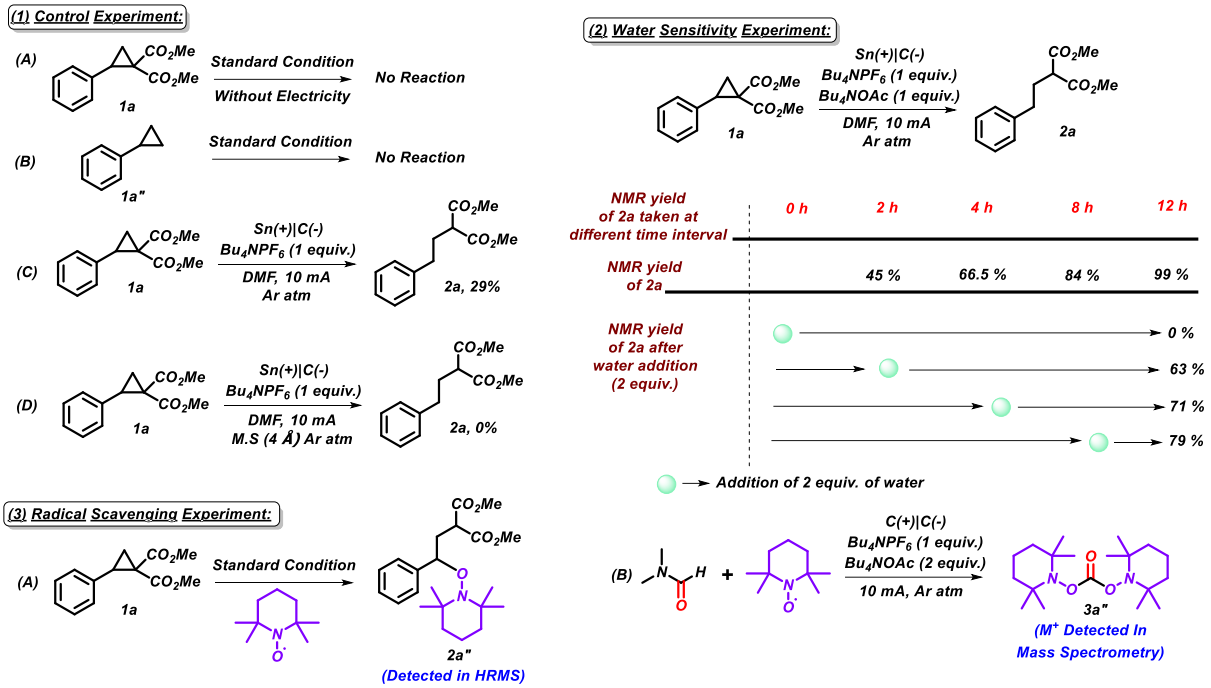


Fig 2. Mechanistic studies (1) Control Experiment (2) Water sensitivity Experiment (3) Radical Scavenging Experiment.

reaction is allowed to continue up to 12 h, and then the NMR yield of the product is taken. Reaction proved to be detrimental in the presence of water. When water is added at the start of the reaction no product formation is observed. During electrolysis, when water is added, the product yield is decreased. From such an experiment, it can be concluded that water trapped in the DMF is not the hydrogen source, but the DMF itself is the hydrogen source. Later, radical scavenging experiments [Fig 2. (3)-(A)] are also performed to check whether the reaction was following a radical pathway or not. When substrate **1a** is subjected to the standard reaction along with TEMPO, **2a"** is detected in the HRMS. We also performed the reaction in the absence of the starting material to check if any radical adduct could be detected from the DMF because DMF acted as a source of hydrogen in the reaction mixture. We are unable to trap this radical adduct under standard conditions. So, we have tried the reaction in the absence of the starting material **1a** and in the presence of carbon electrodes because the sacrificial electrode led to the generation of $Sn(OAc)_2$ in the reaction mixture, which might hinder any adduct formation. We can trap the radical adduct **3a"** due to the electrolysis of DMF with TEMPO as the radical quencher.

Furthermore, a cyclic voltammetry experiment is performed to get more insights into the reaction mechanism. It is revealed that the DAC has a reduction potential of -2.36 V in the presence of electrolytes and additives (Fig 3). Whereas the same in the case of acceptor cyclopropane (AC) is -2.42 V (Fig 3). This provided us with the fact that the reaction might be initiated via the reduction of the ester motif. To bring clarity about this phenomenon, we have further performed the cyclic voltammetry of dimethyl malonate under standard conditions both in the presence of Sn salt and in the absence of it. Interestingly, dimethyl malonate showed an electro-catalytic effect in the presence of Sn^{+2} salt. This not only indicates the reaction is initiated via the ester reduction pathway but also shows the significant role of Sn as a sacrificial anode material. Acetate anion oxidized at 2 V, which plausibly acts as a sacrificial oxidant and facilitates the process in the forward direction.

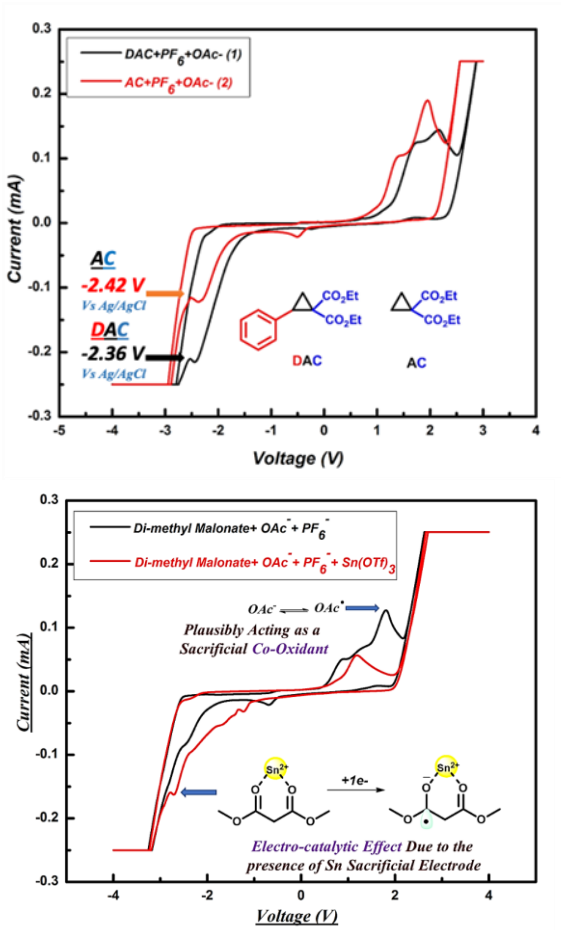
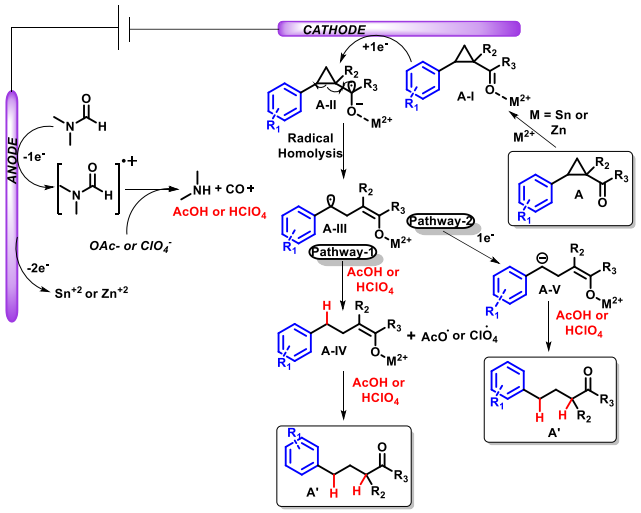


Fig 3. Cyclic Voltammetry Experiment

From the above control experiments and cyclic voltammetry studies, a plausible mechanism is proposed. During electrolysis, the sacrificial electrodes release Sn^{2+} or Zn^{2+} ions in the solution. This Sn^{2+} or Zn^{2+} now coordinated with the oxygen of the carbonyl part of the donor-acceptor cyclopropane or cyclobutane (**A-I**) and facilitated one-electron reduction to generate the intermediate **A-II.** After that, due to the strain in the cyclopropane or cyclobutane moiety, it undergoes a radical homolysis event to generate intermediate **A-III.** DMF oxidized at the anode to generate radical cation intermediate, which further generates AcOH or $HClO_4$ in situ after proton abstraction by the additives or electrolyte salts. After the formation of intermediate **A-III, the** reaction can follow two pathways. Either it underwent another electron transfer event to generate **A-V**, which, after proton exchange from AcOH or $HClO_4$ led to our desired product **A'**. Otherwise, it could follow a second pathway in which intermediate **A-III** underwent a hydrogen atom transfer from the AcOH or $HClO_4$ to generate **A-IV** and regenerate the acetate radical. After that, proton exchange from AcOH or $HClO_4$ led to the formation of our desired product **A'** (Scheme 2).



Scheme 2. Plausible mechanism.

In summary, we have established oxidant-free hydrogenation of DACs and cyclobutane via electrochemical site-selective carbonyl reduction. Control experiments and mechanistic investigations validate the selective reduction of carbonyl led to the ring opening of the strained ring followed by hydrogenation in the presence of in situ generated AcOH or $HClO_4$. The methodology exhibited a wide substrate scope with good functional group tolerance and furnished the desired products in moderate to good yield.

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Keywords: Electrochemistry • Hydrogenation • Reduction • Donor Acceptor Cyclopropane

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