

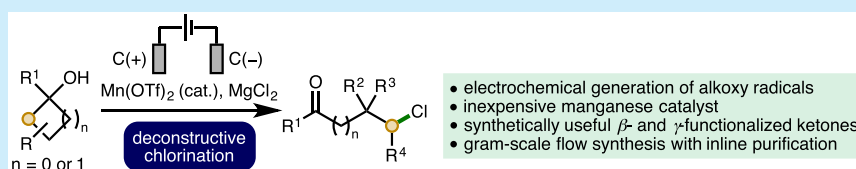
# Manganese-Catalyzed Electrochemical Deconstructive Chlorination of Cycloalkanols via Alkoxy Radicals

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## Supporting Information

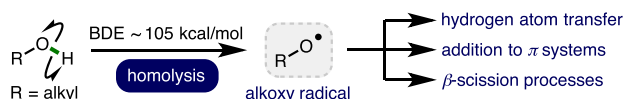


**ABSTRACT:** A manganese-catalyzed electrochemical deconstructive chlorination of cycloalkanols has been developed. This electrochemical method provides access to alkoxy radicals from alcohols and exhibits a broad substrate scope, with various cyclopropanols and cyclobutanols converted into synthetically useful  $\beta$ - and  $\gamma$ -chlorinated ketones (40 examples). Furthermore, the combination of recirculating flow electrochemistry and continuous inline purification was employed to access products on a gram scale.

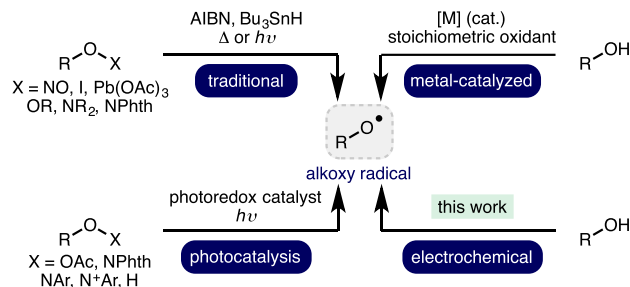
Alkoxy radicals are highly transient species that exhibit diverse reactivity, including hydrogen atom transfer,<sup>1</sup> addition to  $\pi$  systems,<sup>2</sup> and  $\beta$ -scission processes (Scheme 1A).<sup>3</sup> The generation of alkoxy radicals directly from aliphatic alcohols is challenging, partly due to the high dissociation energy of RO–H bonds ( $\sim 105$  kcal/mol).<sup>2b</sup> As such,

## Scheme 1. Context and Outline of Electrochemical Strategy

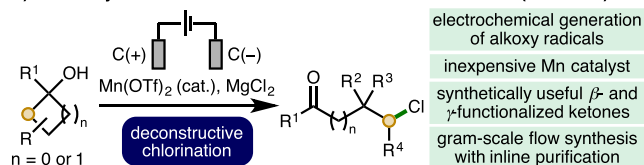
### A) Bond dissociation energy (RO–H) and alkoxy radical reactivity



### B) Generation of alkoxy radicals



### C) Mn-catalyzed electrochemical deconstructive chlorination (this work)



traditional methods for alkoxy radical generation involve the homolysis of weak oxygen-heteroatom bonds within prefunctionalized radical precursors in combination with radical initiators and/or thermal or photochemical activation (Scheme 1B).<sup>1,2</sup> Alternatively, transition metal salts can be employed in combination with stoichiometric oxidants (e.g.,  $K_2S_2O_8$  or hypervalent iodine reagents) for the generation of alkoxy radicals.<sup>4</sup> Recent advances have developed photocatalytic approaches for alkoxy radical generation employing various radical precursors<sup>5</sup> including peroxides,<sup>6</sup> *N*-alkoxyphthalimides,<sup>7</sup> *N*-alkoxypyridiniums,<sup>8</sup> *N*-alkoxybenzimidazoles,<sup>9</sup> *N*-alkoxytriazoliums,<sup>10</sup> and unprotected alcohols.<sup>11</sup> Despite these important advances, many existing approaches require the use of prefunctionalized substrates, (super)stoichiometric reagents (generating waste/byproducts), and/or precious metal (photo)catalysts.

Organic electrochemistry represents one of the cleanest possible chemical processing technologies,<sup>12</sup> which has recently undergone a renaissance due partly to the increasing availability of standardized batch and flow electrochemical reactors.<sup>13</sup> By careful tuning of electrochemical parameters, specific single electron transfer processes can be targeted, accessing powerful radical intermediates.<sup>14</sup> Despite these characteristics, the development of electrochemical methods for the generation of alkoxy radicals from alcohols has received little attention and remains largely limited to the generation of methoxy radicals,<sup>15</sup> which requires expensive boron-doped diamond or platinum anodes.<sup>16</sup> To this end, herein we report

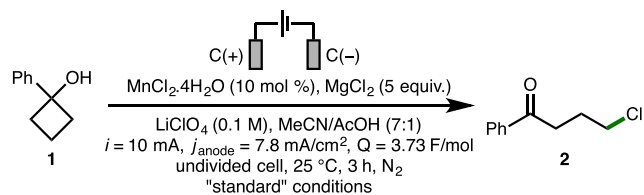
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the manganese-catalyzed electrochemical deconstructive chlorination of cycloalkanols *via* alkoxy radical intermediates,<sup>17</sup> accessing synthetically useful  $\beta$ - and  $\gamma$ -chlorinated ketones (Scheme 1C). Furthermore, by employing microreactor technology and recirculating flow, the electrochemical method can be performed on gram scale, with continuous inline purification incorporated.

To commence our studies, 1-phenylcyclobutan-1-ol **1** was selected as the model substrate (Table 1). After extensive

**Table 1. Optimization of Electrochemical Process<sup>a</sup>**



entry	variation from "standard" conditions	yield <sup>b</sup> (%)
1	none	82
2	no electricity	<2
3	no MnCl <sub>2</sub> ·4H <sub>2</sub> O	<2
4	$E_{\text{cell}} = 2.4 \text{ V}$	66
5	$i = 12.5 \text{ mA}$ , $j_{\text{anode}} = 9.8 \text{ mA/cm}^2$	74
6	$i = 7.5 \text{ mA}$ , $j_{\text{anode}} = 5.9 \text{ mA/cm}^2$	80
7	TBAPF <sub>6</sub> instead of LiClO <sub>4</sub>	82
8	Pt foil cathode instead of graphite	82
9	Ni plate cathode instead of graphite	75
10	Mn(OAc) <sub>2</sub> ·4H <sub>2</sub> O instead of MnCl <sub>2</sub> ·4H <sub>2</sub> O	82
11	Mn(OTf) <sub>2</sub> instead of MnCl <sub>2</sub> ·4H <sub>2</sub> O	97 (78)
12 <sup>c</sup>	LiCl instead of MgCl <sub>2</sub>	64
13 <sup>c</sup>	NaCl instead of MgCl <sub>2</sub>	<2
14 <sup>c</sup>	MgCl <sub>2</sub> (2 equiv)	76
15 <sup>c</sup>	Mn(OTf) <sub>2</sub> (5 mol %)	75
16 <sup>c,d</sup>	$Q = 2 \text{ F/mol}$	67

<sup>a</sup>Reactions performed with 0.3 mmol of cyclobutanol **1** using the ElectraSyn 2.0 batch electrochemical reactor. [1] = 0.05 M. <sup>b</sup>Yield after 3 h as determined by <sup>1</sup>H NMR analysis of the crude reaction mixture with 1,3,5-trimethylbenzene as the internal standard. Isolated yield given in parentheses. <sup>c</sup>Mn(OTf)<sub>2</sub> as catalyst. <sup>d</sup>96 min reaction time.

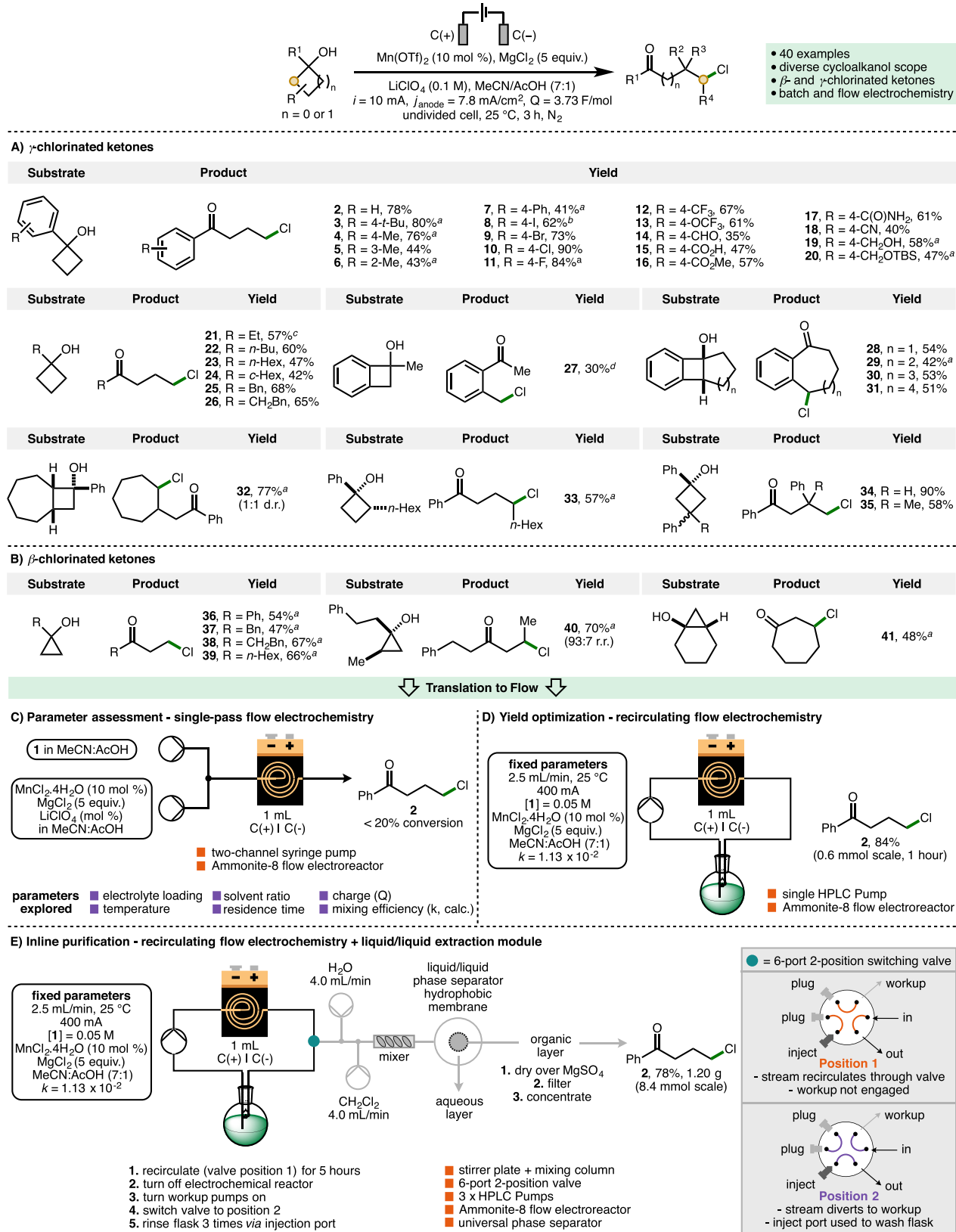
optimization,<sup>18</sup> it was found that an electrochemical system composed of MnCl<sub>2</sub>·4H<sub>2</sub>O (10 mol %) as catalyst,<sup>19</sup> MgCl<sub>2</sub> (5 equiv) as chloride source, and LiClO<sub>4</sub> as supporting electrolyte in MeCN/AcOH (7:1, [1] = 0.05 M) using galvanostatic conditions ( $i = 10 \text{ mA}$ ,  $j_{\text{anode}} = 7.8 \text{ mA/cm}^2$ ,  $Q = 3.73 \text{ F/mol}$ ) and graphite electrodes at 25 °C for 3 h under N<sub>2</sub>, enabled the deconstructive chlorination of **1**, giving  $\gamma$ -chlorinated ketone **2** in 82% NMR yield (entry 1). No conversion occurs in the absence of electricity or the manganese catalyst (entries 2 and 3). Employing a constant cell potential ( $E_{\text{cell}} = 2.4 \text{ V}$ ) or variation of the current ( $i = 12.5 \text{ mA}$  or  $7.5 \text{ mA}$ ) lowered the NMR yield of **2** (entries 4–6). Employing TBAPF<sub>6</sub> as electrolyte (entry 7) or substituting the graphite cathode for Pt foil or Ni plate (entries 8 and 9) each had a negligible impact on conversion. However, upon evaluating alternative Mn(II) salts (entries 10 and 11), it was found that 97% conversion was obtained using Mn(OTf)<sub>2</sub> as catalyst, which was adopted for further optimization. Employing LiCl or NaCl as the chloride source was detrimental to conversion, presumably due to decreased solubility in MeCN/AcOH (entries 12 and 13).<sup>20</sup> Gratifyingly, the quantities of MgCl<sub>2</sub> and

Mn(OTf)<sub>2</sub> could be lowered to 2 equiv and 5 mol %, respectively, without significant reduction in conversion (entries 14 and 15). A Faradaic efficiency of 67% was obtained when 2 F/mol of charge was passed (entry 16), which indicated that most of the electricity passing through the cell is utilized productively.

The full scope of the electrochemical process was explored starting with the deconstructive chlorination of cyclobutanols to form  $\gamma$ -functionalized ketones (Scheme 2A). From the outset, it was found that 1-arylcyclobutan-1-ols containing aromatic systems with electron-releasing groups at the 2- or 4-positions (e.g., 4-*t*Bu) or extended  $\pi$  systems (e.g., 4-Ph) undergo decomposition using the optimized reaction conditions (Table 1, entry 11). This instability was attributed to ionization of the C–OH bond in the presence of Brønsted and/or Lewis acids, forming stabilized carbocations that are unproductive for the desired transformation. In such cases, this issue was addressed by employing syringe pump addition of the substrate over 2 h and using TBAOAc as the supporting electrolyte. With a choice of two suitable reaction conditions in hand, a variety of 1-arylcyclobutan-1-ols were converted to the corresponding  $\gamma$ -chlorinated ketone products in good to excellent isolated yields (products 2–20). Within the aryl unit, various alkyl and aryl substitution was tolerated at the 4-, 3-, and 2-positions in addition to halides and electron-withdrawing substituents (e.g., 4-CF<sub>3</sub>). The electrochemical method exhibits good functional group tolerance as demonstrated by the presence of aldehyde, carboxylic acid, methyl ester, primary amide, nitrile, benzylic primary alcohol, and silyl ether functionalities present within products 14–20. A selection of 1-alkylcyclobutan-1-ols were also converted into the corresponding  $\gamma$ -chlorinated ketones in good isolated yields (products 21–26). Benzo-fused cyclobutanols participated in deconstructive chlorination, giving benzyl chloride products 27–31, including the formation of 7-, 8-, 9-, and 10-membered rings. This strategy was also applied to the formation of disubstituted cycloheptane **32** in 77% isolated yield. Additional substitution at the 2- and 3-positions of the cyclobutanol was tolerated, accessing  $\gamma$ -chlorinated ketones 33–35 in high yields. We also investigated the deconstructive chlorination of cyclopropanols (Scheme 2B). Gratifyingly, it was found that a representative selection of 1-arylcyclopropan-1-ols and 1-alkylcyclopropan-1-ols could be readily converted to the corresponding  $\beta$ -chlorinated ketones in good yields (36–39). Additional substitution is tolerated within the cyclopropanol, giving secondary radical derived product **40** as the major regioisomer. Furthermore, bicyclo[4.1.0]heptan-1-ol was converted to 3-chlorocycloheptan-1-one **41** in 48% isolated yield. At the current stage of development, the electrochemical method does not tolerate larger ring sizes with reduced ring strain. For example, despite assessing various reaction conditions, 1-phenylcyclopentan-1-ol underwent decomposition, whereas 1-phenethylcyclopentan-1-ol was unreactive.<sup>21</sup>

In order to demonstrate scalability, the batch process was translated to a flow electrochemical setup.<sup>22</sup> By employing the commercially available Ammonite8 flow electroreactor,<sup>23</sup> a variety of reaction parameters were evaluated including electrolyte loading, temperature, solvent ratio, residence time, charge, and mixing efficiency (Scheme 2C). However, by using MnCl<sub>2</sub>·4H<sub>2</sub>O (10 mol %) as catalyst, the conversion to **2** could not be increased beyond 20% using single-pass flow electrochemistry.<sup>18</sup> The yield was increased by applying the optimized reaction parameters to a recirculating flow electrochemical

## Scheme 2. Substrate Scope: Batch and Flow Electrochemistry\*



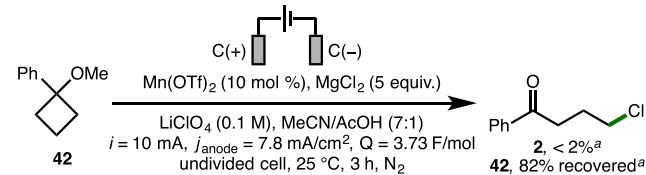
\*Reactions performed with 0.3 mmol of cycloalkanol using the ElectraSyn 2.0 batch electrochemical reactor with isolated yields after chromatographic purification quoted unless stated otherwise. <sup>a</sup>Cycloalkanol was added over 2 h via syringe pump, TBAOAc (0.1 M) as electrolyte. <sup>b</sup>TBAOAc (0.1 M) as electrolyte. <sup>c</sup>Yield as determined by <sup>1</sup>H NMR analysis of the crude reaction mixture with 1,3,5-trimethylbenzene as the internal standard. <sup>d</sup>6 h.

setup, which provided access to **2** in 84% isolated yield (Scheme 2D).<sup>24</sup> Advantageously, due to the decreased distance between the electrodes in flow, a supporting electrolyte was not required. Furthermore, by employing a 6-port 2-position switching valve, the flow could be redirected from recirculation to continuous inline purification (Scheme 2E). Once the electrochemical reaction was complete, the valve was switched from position 1 to position 2 to redirect the flow into the path of workup solvents. The flow was passed through a mixing unit before entering a liquid/liquid phase separator containing a hydrophobic membrane that allowed separation of the organic layer, which was subsequently dried over MgSO<sub>4</sub>, filtered, and concentrated in vacuo to provide 1.2 g of product. This flow setup, which combines recirculating flow electrochemistry and continuous inline purification for the first time, might be suitable for >1 g scale processing by increasing reactor volume and operation time.

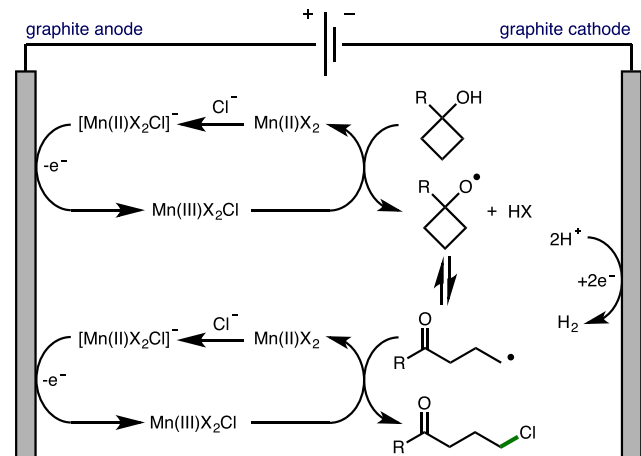
Cyclic voltammetry was employed in order to gain mechanistic insight into the electrochemical process.<sup>18</sup> In accordance with the literature,<sup>19d</sup> the combination of Mn(OTf)<sub>2</sub> and MgCl<sub>2</sub> produced a new quasi-reversible redox event at ~0.8 V vs Fc/Fc<sup>+</sup>,<sup>25</sup> which provided evidence for the generation of a Mn(III)X<sub>2</sub>Cl species from [Mn(II)X<sub>2</sub>Cl]<sup>-</sup>. Furthermore, an increase in the oxidation current was observed upon addition of 1-phenylcyclobutan-1-ol **1**, which suggested that Mn(III)X<sub>2</sub>Cl is consumed by **1**. When methyl ether cyclobutane **42** was employed as the substrate using the standard electrochemical reaction conditions, no  $\gamma$ -chlorinated ketone **2** was observed, with 82% starting material recovered (Scheme 3A). This indicated that the proposed Mn(III)X<sub>2</sub>Cl species does not promote cyclobutane ring opening in the absence of a hydroxyl functional group. As such, a plausible reaction mechanism initiates with the formation of

### Scheme 3. Mechanistic Studies

#### A) Mechanistic probe using methyl ether substrate



#### B) Plausible reaction mechanism



<sup>a</sup>Yield as determined by <sup>1</sup>H NMR analysis of the crude reaction mixture with 1,3,5-trimethylbenzene as the internal standard.

[Mn(II)X<sub>2</sub>Cl]<sup>-</sup> from Mn(II)X<sub>2</sub> and MgCl<sub>2</sub>, which is oxidized at the anode to form Mn(III)X<sub>2</sub>Cl (Scheme 3B). This intermediate undergoes ligand exchange with the cycloalkanol to form a Mn(III) alkoxide, with subsequent homolysis generating an alkoxy radical, which can undergo reversible  $\beta$ -scission. Alternatively, the Mn(III) alkoxide may undergo reversible  $\beta$ -scission, rather than a free alkoxy radical intermediate. Trapping of the transient primary carbon-centered radical with the persistent Mn(III)X<sub>2</sub>Cl species forms a new C–Cl bond.<sup>26</sup> Hydrogen gas is generated via proton reduction at the cathode.

In conclusion, we have developed a new electrochemical method for alkoxy radical generation from alcohols and utilized this for the manganese-catalyzed electrochemical deconstructive chlorination of cycloalkanols. The method is applicable across various cyclopropanols and cyclobutanols, accessing a broad range of synthetically useful  $\beta$ - and  $\gamma$ -chlorinated ketones (40 examples). Furthermore, the combination of recirculating flow electrochemistry and continuous inline purification was employed to access products on gram scale. Ongoing studies are focused on further applications of earth-abundant transition metals in synthetic organic electrochemistry, and these results will be reported in due course.<sup>27</sup>

### ■ ASSOCIATED CONTENT

#### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b03652.

Optimization data, experimental procedures, characterization of new compounds and spectral data (PDF)

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#### Notes

The authors declare no competing financial interest. Information about the data that underpins the results presented in this article, including how to access them, can be found in the Cardiff University data catalogue at <http://doi.org/10.17035/d.2019.0087324419>.

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