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## Accepted Article

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# Scalable and Practical Electrooxidation of Electron-Deficient Methylarenes to Access Aromatic Aldehydes

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**Abstract:** Aromatic aldehydes are pivotal synthetic intermediates with applications in fine chemicals, pharmaceuticals, agrochemicals, and advanced materials. While the oxidation of methylarenes represents an ideal route to aromatic aldehydes due to the availability of starting materials, existing methods face significant challenges, including reliance on hazardous oxidants, costly catalysts, poor scalability, and limited compatibility with electron-deficient substrates. To address these limitations, we report a practical and scalable electrochemical method for the oxidation of electron-deficient methylarenes to access aromatic aldehydes, eliminating the need for chemical oxidants or homogeneous transition-metal catalysts. This approach operates under industrially viable conditions—high current densities (75 mA cm<sup>-2</sup>), minimal electrolyte loading (0.05 equiv), and operation in an undivided cell without additives—to produce aromatic acetals, which are readily hydrolyzed to the corresponding aldehydes. The use of minimal electrolyte not only reduces costs and simplifies product isolation but also significantly enhances anodic oxidation selectivity, ensuring high efficiency and practicality. This protocol exhibits a broad substrate scope, compatibility with both batch and continuous flow systems, and exceptional scalability, as demonstrated by successful

kilogram-scale synthesis.

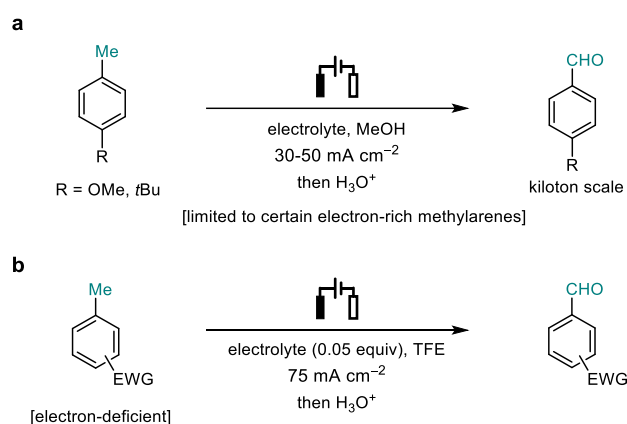
## Main Text

Aromatic aldehydes are indispensable intermediates in the synthesis of fine chemicals, pharmaceuticals, agrochemicals, and advanced materials.<sup>[1]</sup> Their preparation via the oxidation of methylarenes represents an ideal strategy due to the commercial availability and ease of handling of these precursors. However, achieving selective oxidation remains a formidable challenge, particularly for electron-deficient methylarenes, which exhibit reduced reactivity.

Traditional methods for methylarene oxidation rely heavily on stoichiometric oxidants such as chromium, cerium, or hypervalent iodine reagents, raising significant environmental and safety concerns.<sup>[2-4]</sup> Catalytic approaches, while more sustainable, often require expensive metal complexes as catalysts, along with hazardous oxidants like Selectfluor, K<sub>2</sub>S<sub>2</sub>O<sub>8</sub>, or peroxides.<sup>[5-7]</sup> Aerobic oxidation strategies, though promising, are hindered by issues such as overoxidation to carboxylic acids, poor reactivity with electron-deficient substrates, and the complexities of oxygen management at scale.<sup>[8-11]</sup> Consequently, industry continues to rely on indirect halogenation-oxidation/hydrolysis sequences,<sup>[1, 12-15]</sup> which involve hazardous reagents and often yield undesirable mixed halogenation products.<sup>[14]</sup>

Electrochemistry has emerged as a sustainable synthetic tool that replaces chemical redox reagents with traceless electrons<sup>[16-29]</sup> and have been applied to the oxygenation of alkylarenes.<sup>[30-34]</sup> Notably, the electrooxidation of electron-rich toluene derivatives has been successfully implemented in the industrial production of *p*-anisaldehyde and 4-*tert*-butylbenzaldehyde (Fig. 1a).<sup>[35]</sup> However, extending this methodology to electron-deficient methylarenes has proven challenging due to their

higher oxidation potentials and susceptibility to side reactions, such as aromatic ring substitution.<sup>[36-38]</sup> Recent advances in the electrochemical oxidation of electron-deficient methylarenes, such as NHPI-mediated protocols, expand substrate scope but reintroduce stoichiometric reagents and multi-step processes.<sup>[36]</sup> Alternatively, electrochemical aerobic systems can promote this transformation but face inherent safety concerns, primarily stemming from the generation of explosive O<sub>2</sub>/H<sub>2</sub> gas mixtures during electrolysis, operation at low current densities (<10 mA cm<sup>-2</sup>), and reliance on high concentrations of electrolyte salts.<sup>[39, 40]</sup> These limitations not only undermine the benefits of electrochemistry but also collectively constrain production rates and restrict industrial applications.



**Fig. 1 Synthesis of aromatic aldehydes via electrochemical oxidation of methylarenes. a.** Industrial electrochemical oxidation for kiloton scale production of 4-anisaldehyde and 4-*tert*-butylbenzaldehyde. **b.** Electrochemical oxidation of electron-deficient methylarenes for the synthesis of aromatic aldehydes. EWG, electron-withdrawing group. TFE, 2,2,2-trifluoroethanol.

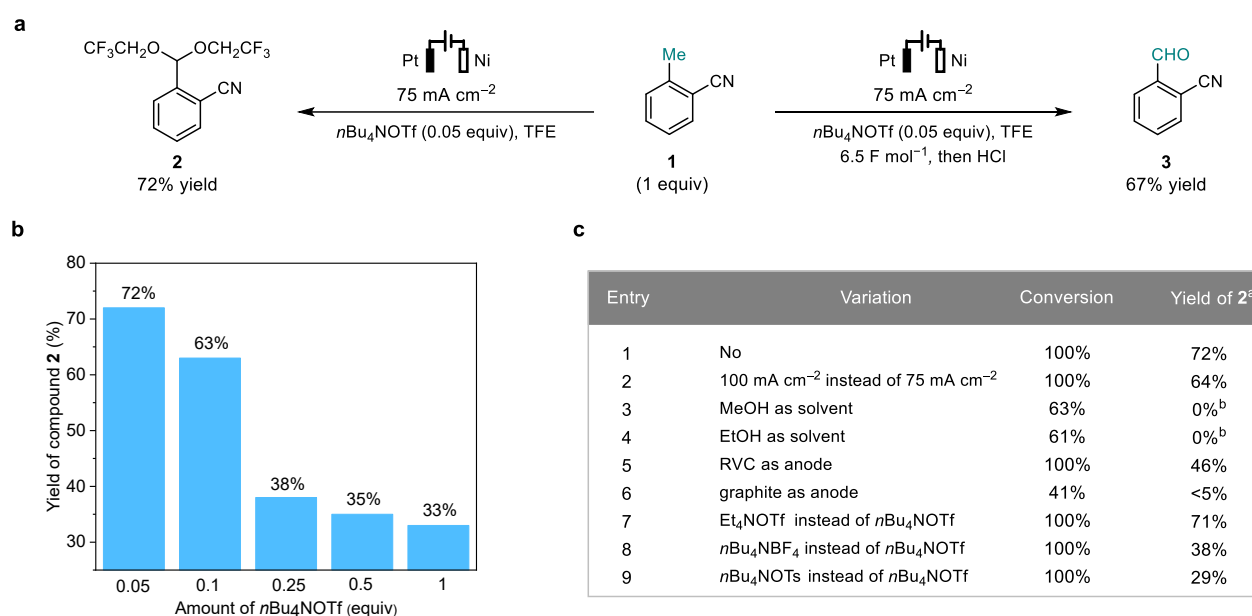
Given these challenges, there remains a critical need for scalable and environmentally benign methods—ideally free of chemical oxidants—to convert electron-deficient methylarenes into aromatic aldehydes. We have been exploring the electrochemical oxidation of alkylarenes<sup>[41]</sup> and previously achieved the selective electrochemical oxidation of relatively electron-rich polymethyl-substituted benzimidazoles employing methanol as solvent.<sup>[37]</sup> In this study, we address these challenges by

introducing a scalable and practical electrochemical strategy for the oxidation of electron-deficient methylarenes to aromatic acetals, which can be readily hydrolyzed to aromatic aldehydes (Fig. 1b). Our method employs industrially relevant conditions—high current densities ( $75 \text{ mA cm}^{-2}$ ) in undivided cells, minimal electrolyte loading (0.05 equiv), and an additive-free environment—to achieve selective benzylic oxidation without the need for homogeneous metal catalysts or hazardous reagents. The protocol demonstrates broad substrate tolerance, accommodating sterically hindered and poly-substituted methylarenes. Scalability is demonstrated through batch reactions at 100 g and kilogram scales, as well as continuous flow processes. Central to the success of this electrochemical approach is the use of low electrolyte concentrations to enhance the selectivity of anodic oxidation and 2,2,2-trifluoroethanol (TFE) as a solvent, which resists oxidative decomposition and minimizes undesired aromatic ring substitution.

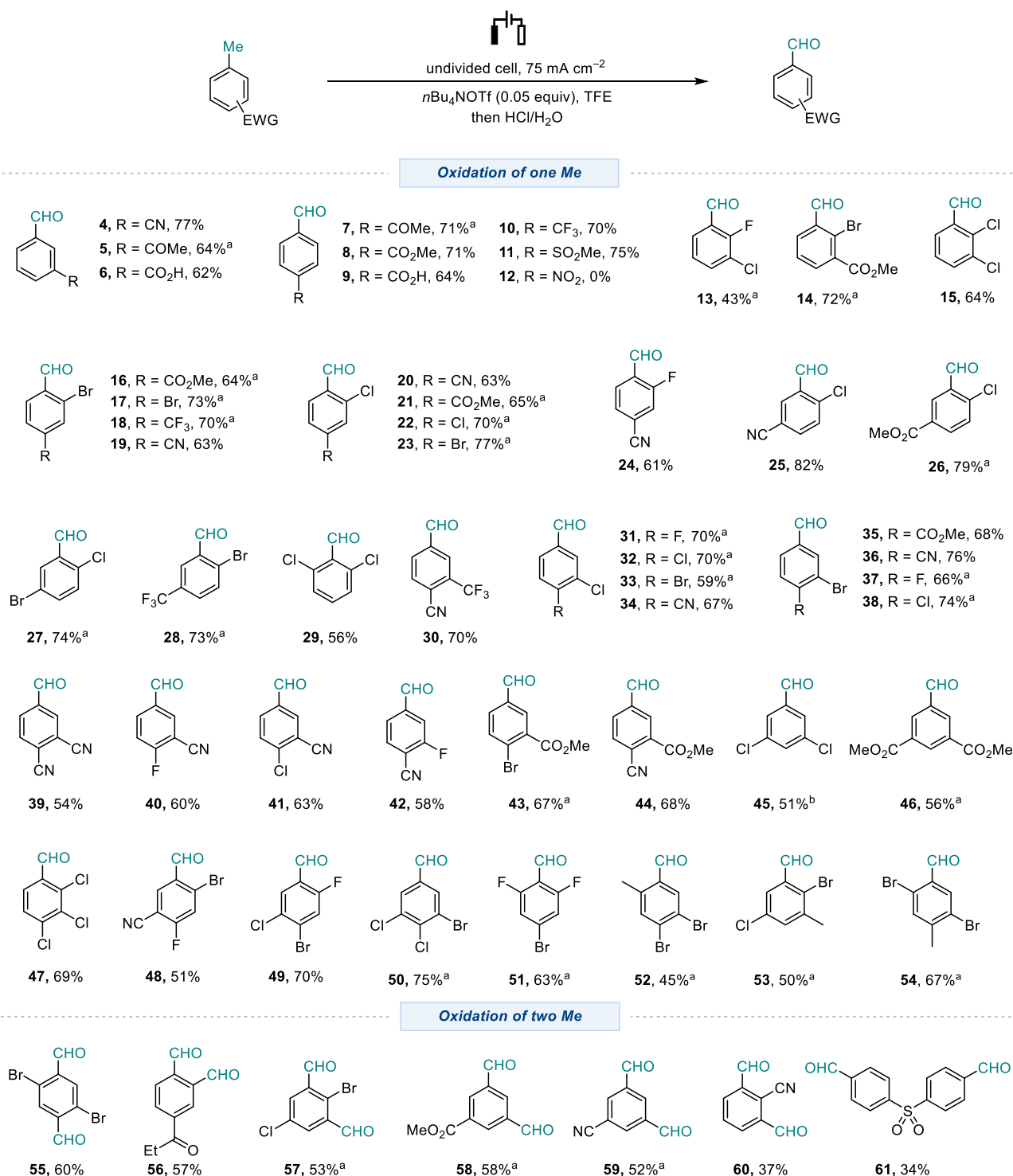
The electrochemical oxidation of 2-methylbenzonitrile (**1**) was selected as a model reaction to establish optimal conditions (Fig. 2a). Under industrially relevant current densities ( $75 \text{ mA cm}^{-2}$ ) in an undivided cell, the desired acetal **2** was obtained in 72% yield using trifluoroethanol (TFE) as the solvent and a minimal electrolyte loading (0.05 equiv of  $n\text{Bu}_4\text{NOTf}$ ). Subsequent treatment of the post-electrolysis mixture with aqueous HCl furnished benzaldehyde **3** in 67% yield. Notably, the high current density ensures scalability and productivity, while the low electrolyte concentration minimizes costs, simplifies product isolation, and facilitates solvent recycling—critical advantages for industrial adoption.

Counterintuitively, increasing the electrolyte concentration significantly reduced the yield of **2** (Fig. 2b). Similarly, elevating the current density to  $100 \text{ mA cm}^{-2}$  marginally decreased the yield

to 64% (Fig. 2c, entry 2). Solvent screening revealed that methanol or ethanol (entries 3–4) completely suppressed acetal product formation due to competitive solvent oxidation. Among anode materials, platinum outperformed carbon-based electrodes (entries 5–6), which rapidly passivated due to the high oxidation potential of the methylarene **1**. Notably, Pt-coated titanium (Pt@Ti) can be used as a cost-effective alternative (vide infra). The choice of electrolyte also influenced the yields: while *n*Bu<sub>4</sub>NOTf and Et<sub>4</sub>NOTf (entry 7) performed similarly, *n*Bu<sub>4</sub>NBF<sub>4</sub> (entry 8) and *n*Bu<sub>4</sub>NOTs (entry 9) were less effective.



**Fig. 2 Reaction development for the electrochemical oxidation of methylarene 1.** **a.** Optimized reaction conditions for the electrochemical oxidation of methylarene **1**. **b.** Assessment of the effect of *n*Bu<sub>4</sub>NOTf concentration on the yield of acetal **2**. Complete conversion for all entries. **c.** Control experiments for the electrochemical oxidation of **1**. <sup>a</sup>Yield based on <sup>1</sup>H NMR analysis. <sup>b</sup>Yield of the corresponding solvent-derived acetal. *n*Bu<sub>4</sub>NOTf, tetrabutylammonium trifluoromethanesulfonate.



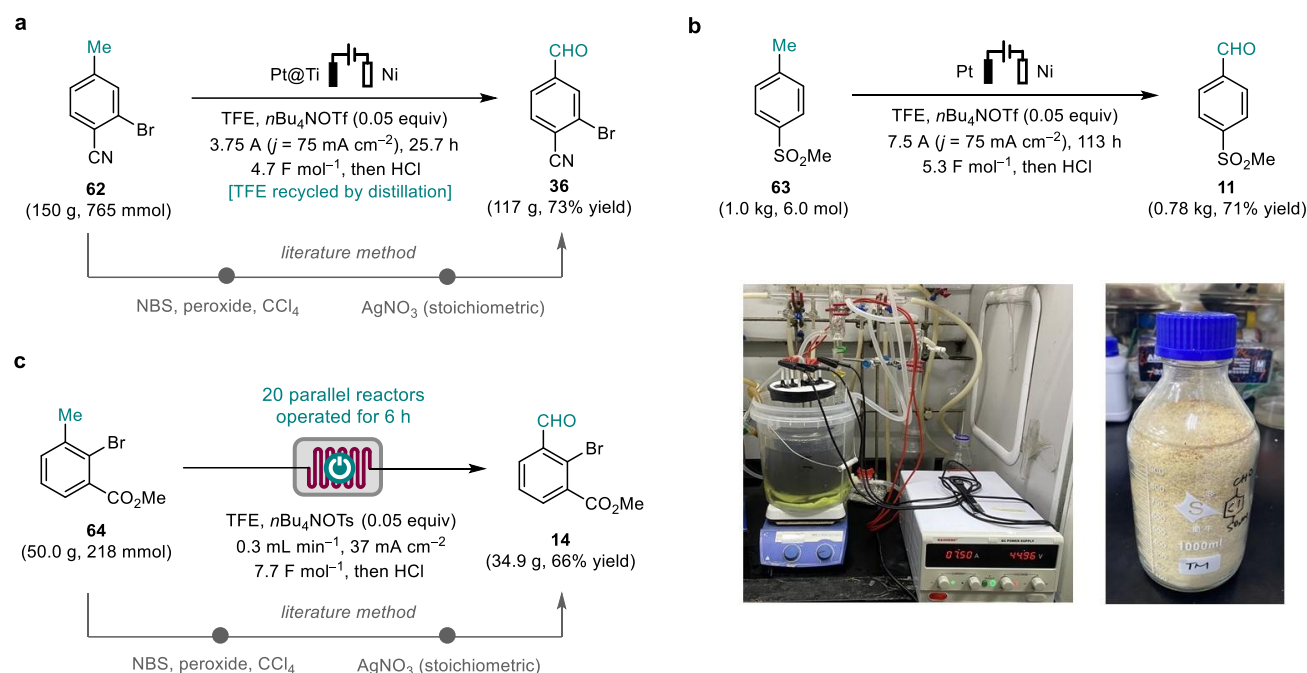
**Fig. 3 Substrate scope of methylarenes.** Reaction conditions: alkylarene (1.0 mmol), TFE (5 mL), *n*Bu<sub>4</sub>NOTf (0.05 mmol); then HCl (4 M, 1.5 mL), reflux. Yields are reported for the isolated aldehydes. <sup>a</sup>*n*Bu<sub>4</sub>NOTs was used as electrolyte instead of *n*Bu<sub>4</sub>NOTf. <sup>b</sup>NaOTf (10 mol%) was used as electrolyte instead of *n*Bu<sub>4</sub>NOTf.

The electrochemical protocol demonstrated broad applicability to electron-deficient methylenes with diverse substitution patterns (Fig. 3). Meta- and para-substituted toluenes (e.g., **4**–**11**) were successfully oxidized, though nitro-substituted substrates (e.g., **12**) failed, likely due to competitive cathodic nitro group reduction. Di- and tri-substituted derivatives, including sterically demanding 2,6-dichlorotoluene (**29**) and highly electron-deficient analogs bearing dual cyano (**39**) or ester (**46**) groups, were also viable. Remarkably, substrates with two methyl groups underwent selective mono-oxidation (**52**–**54**) or, upon application of a higher charge, full oxidation to bisaldehydes (**55**–**61**), the latter of which remains challenging for conventional methods due to overoxidation. Some substrates, particularly those less electron-deficient than the model nitrile substrate **1**, experienced unwanted substitution at the benzene ring. However, these issues were mitigated using *n*Bu<sub>4</sub>NOTs as the electrolyte. The more basic tosylate likely facilitated benzylic deprotonation, steering the reaction towards benzylic functionalization rather than benzene ring substitution. By contrast, heteroaromatic substrates such as methylated pyridines and pyrimidine did not afford the desired products, indicating a limitation of the current method for electron-deficient heteroarenes (see Figure S6 in the Supporting Information for details).

Successful scale-up was demonstrated through both batch and continuous flow methodologies. In batch mode, the 100 g-scale oxidation of **62** using Pt@Ti anodes (designed to minimize platinum usage) afforded aldehyde **36** in 73% isolated yield (Fig. 4a), maintaining fidelity with small-scale performance (76% yield), thereby validating process robustness. Notably, direct kilogram-scale electrolysis of **63** under identical conditions delivered aldehyde **11** in 71% yield without requiring parameter reoptimization (Fig. 4b), underscoring exceptional translational consistency. This

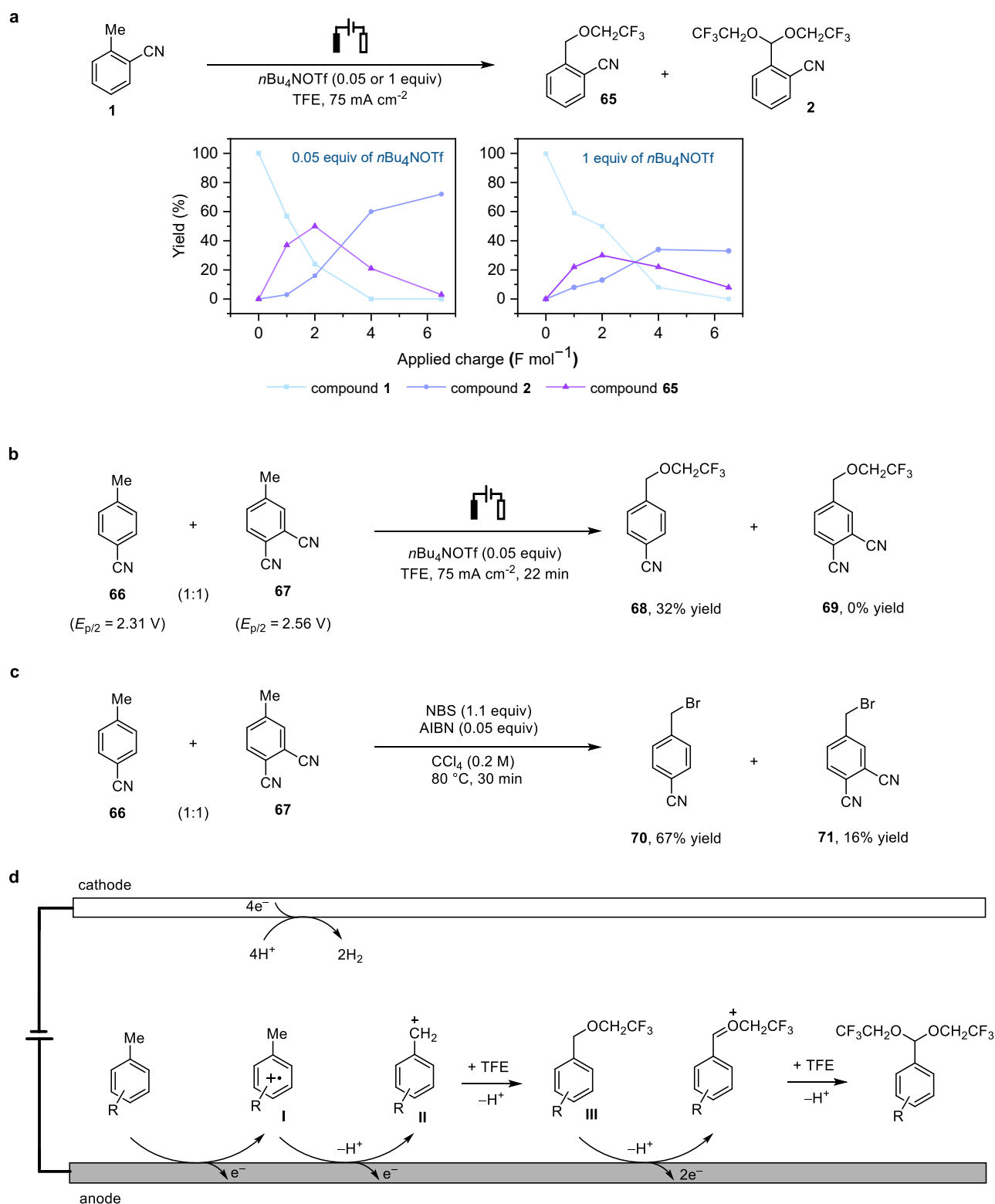


experiment also demonstrated the long-term stability of the electrochemical system. The reaction time for kilogram production could be shortened by increasing the electrode surface area while maintaining a constant current density. For continuous processing, a six-hour operation of compound **64** oxidation was achieved by implementing a modular system of 20 parallel microreactors, producing 34.9 g of aldehyde **14** (66% yield, Fig. 4c). This continuous-flow electrochemical reactor configuration, arranged in parallel, was selected to avoid the engineering challenges associated with direct geometric scale-up, such as elevated ohmic resistance and impaired mass and heat transfer, thereby maintaining optimal electrochemical performance and enabling higher efficiency for large-scale electrochemical synthesis. This electrochemical platform eliminates dependence on toxic stoichiometric oxidants (e.g., NBS and peroxide) and silver-containing reagents mandated by prior protocols,<sup>[42, 43]</sup> while sustaining efficiency across scales. In addition, the TFE solvent used in this process was readily recovered by simple distillation. For the process shown in Fig. 4a, 88% of the TFE was recovered by simple distillation. The electrolysis of compound **1** with recovered TFE afforded compound **2** in 71% yield under standard conditions without any reduction in electrochemical efficiency.



**Fig. 4 Reaction scale-up.** **a.** Hundred-gram scale reaction in batch. **b.** Kilogram scale reaction in batch. **c.** Continuous production with twenty parallel microreactors.

Reaction monitoring revealed that methyllarene **1** first converted to ether intermediate **65**, which subsequently transformed into acetal **2** (Fig. 5a). At low electrolyte concentrations (0.05 equiv of  $n\text{Bu}_4\text{NOTf}$ ), **2** accumulated as **1** and **65** were consumed. Conversely, high electrolyte loading (1 equiv) led to oxidative decomposition of **2**, likely due to reduced selectivity between oxidation of **1/65** and **2**. Cyclic voltammetry suggested that **2** oxidizes at a slightly higher potential than **65** (See Supporting the Information for details). Since redox potentials are influenced by electrolyte concentration, this potential gap likely widens under dilute conditions, providing a plausible explanation for the enhanced selectivity observed at lower electrolyte concentrations.



**Fig. 5 Mechanistic studies and proposal.** **a.** Reaction progress of the electrolysis of **1** in the presence of 0.05 or 1 equiv of  $n\text{Bu}_4\text{NOTf}$ . **b.** Electrochemical oxidation of a mixture of **66** and **67**. **c.** Radical based bromination of a mixture of **66** and **67**. **d.** Proposed mechanism for the electrochemical oxidation of methyl arenes. NBS, N-Bromosuccinimide. AIBN, azobisisobutyronitrile.

Competitive electrolysis of methylarenes **66** (lower oxidation potential) and **67** (higher oxidation potential) yielded only ether **68** (from **66**) (Fig. 5b), whereas thermal bromination with NBS/AIBN produced both benzyl bromides **70** and **71** (Fig. 5c). This stark contrast supports an electron transfer-driven mechanism for the electrochemical process, distinct from the radical-based pathway of thermal bromination.

Building on these findings, we propose a stepwise mechanism for the electrochemical oxidation of methylarenes (Fig. 5d). Initial single-electron transfer at the anode generates an arene radical cation intermediate (**I**), which undergoes sequential proton and electron transfer to form a benzylic carbocation (**II**). Nucleophilic trapping of **II** by TFE solvent yields the benzyl ether intermediate (**III**). A subsequent oxidation cycle—involving analogous electron transfer, proton/electron transfer, and TFE addition—converts **III** to the final acetal product. Compared to MeOH, TFE is more resistant to oxidative decomposition and less nucleophilic. The use of TFE as the solvent ensures selective oxidation of the electron-deficient methylarene substrates and minimizes unwanted solvent trapping of the arene radical cation intermediates.

In summary, we developed a scalable, electrochemical method for oxidizing electron-deficient methylarenes to access benzaldehydes under industrially viable conditions. Key features—low electrolyte loading, additive-free operation, high current density, and compatibility with batch/flow systems—address longstanding challenges in aromatic aldehyde synthesis. This work bridges a critical gap in sustainable aromatic aldehyde synthesis, offering a robust, industrially adaptable solution that circumvents longstanding practical limitations in selectivity, safety, and scalability.

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**Author contributions:** C.H. performed the experiments and analyzed the data. H.C.X. directed the project and wrote the manuscript with contributions from all authors.

**Data availability.** The data supporting the findings of this study are available within the article and its Supplementary Information files.

**Supplementary Information** is available.

**Competing interests:** The authors declare no competing interests.

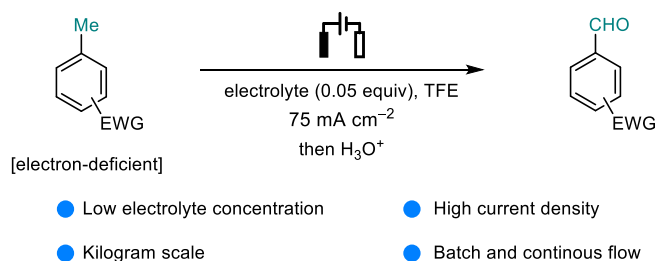
**Keywords:** electrochemistry; aldehyde; oxidation; C-H functionalization; synthetic methods

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## TOC



Report herein is a practical and scalable electrochemical method for the oxidation of electron-deficient methylarenes to access aromatic aldehydes, eliminating the need for chemical oxidants or homogeneous transition-metal catalysts. This approach demonstrates exceptional performance under industrially viable conditions—high current densities, minimal electrolyte loading, and operation in an undivided cell without additives.