

RESEARCH ARTICLE

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Electrosynthesis is an efficient and powerful tool for the generation of elusive reactive intermediates. The application of alternative electrolysis waveforms provides a new level of control for dynamic redox environments. Herein, we demonstrate that pulsed electrolysis provides a favourable environment for the generation and fluorination of highly unstable primary benzylic cations from C(sp³)-H bonds. By introduction of a *t*_{off} period, we propose this waveform modulates the electrical double layer to improve mass transport and limit over-oxidation.

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Organic electrochemistry offers unique control of redox reactions through the ability to accurately control potentials and rates, which has several advantages for selectivity and sustainability in synthesis.^{1–4} Electrochemical anodic oxidation and cathodic reduction is demonstrated as a means of generating highly reactive intermediates,^{5–8} including, ionic species, radicals (cations/anions), and reactive metal complexes (Fig. 1A). These intermediates are useful and important for myriad synthetic transformations,^{5,9} and can be uniquely generated from starting materials without pre-functionalisation using electrochemistry.

An elusive and particularly reactive intermediate is the primary benzylic cation. Electrochemical oxidation has been demonstrated as an efficient means of producing benzylic cations from benzylic C(sp³)-H bonds, *via* a sequential electron-transfer, proton-transfer, electron-transfer (ET/PT/ET) sequence.^{10–17} Without the stabilisation that hyperconjugation provides, primary are less stable than secondary, which are less stable than tertiary benzylic cations, Fig. 1B. Hence, in contrast to secondary and tertiary, the generation of primary benzylic cations by electrochemical oxidation and their functionalisation has been reported very few times, and as such is limited to the use of highly electron-rich substrates, solvent level nucleophile, or a cation-pool strategy.^{18–23}

The introduction of alternative electrolysis waveforms has been demonstrated as a tool for facilitating unique reactivity (Fig. 1C).^{24–26} For example, alternating polarity has enabled

new reactivity and selectivity, including reactions of short-lived species *via* paired-electrolysis,²⁷ unique chemoselectivity for reductions,^{28,29} or selective control over one- or two-electron reactivity,³⁰ demonstrating the additional level of control that can be enabled by dynamic redox environments using an electrochemical strategy.

Within this vein, we were interested to investigate how alternative waveforms might influence the generation and functionalisation of primary benzylic cations. Despite the strategically facile nature of generating reactive species electrochemically, it does not come without challenges. These include undesired side-reactions and electrode-grafting/fouling processes that add to the difficulty and complexity.³¹ Specifically, we hypothesized that dynamic manipulation of the electrical double layer may aid their desired functionalization and avoid side-reactions. This unique electrode-surface environment can be altered with the applied potential (fixed or moving), electrode material, electrolyte composition and mass transfer regimes, which all influence the outcome of the reaction.^{32–38}

We elected to conduct these fundamental studies on the formation and functionalisation of primary benzylic cations from C(sp³)-H bonds using fluorination as a test reaction. Benzylic and aliphatic fluorides have been realised *via* photochemical,^{39–43} radical^{44–50} and metal-catalysed strategies^{51–55} from C-H bonds, as well as decarboxylative routes.^{56–60} However, the nucleophilic fluorination of benzylic C(sp³)-H bonds *via* cationic intermediates is a highly challenging transformation; current methods are limited and almost entirely focussed on secondary and tertiary benzylic C(sp³)-H bonds,^{42,43,61,62} with only two prior reports showing examples of primary, Fig. 1D.^{20,21} Fuchigami demonstrated only toluene as a suitable substrate, in which Ritter-amination competed, and Middleton demonstrated that benzylic fluorination competes with C(sp²)-H ring fluorination on a set of electron-poor

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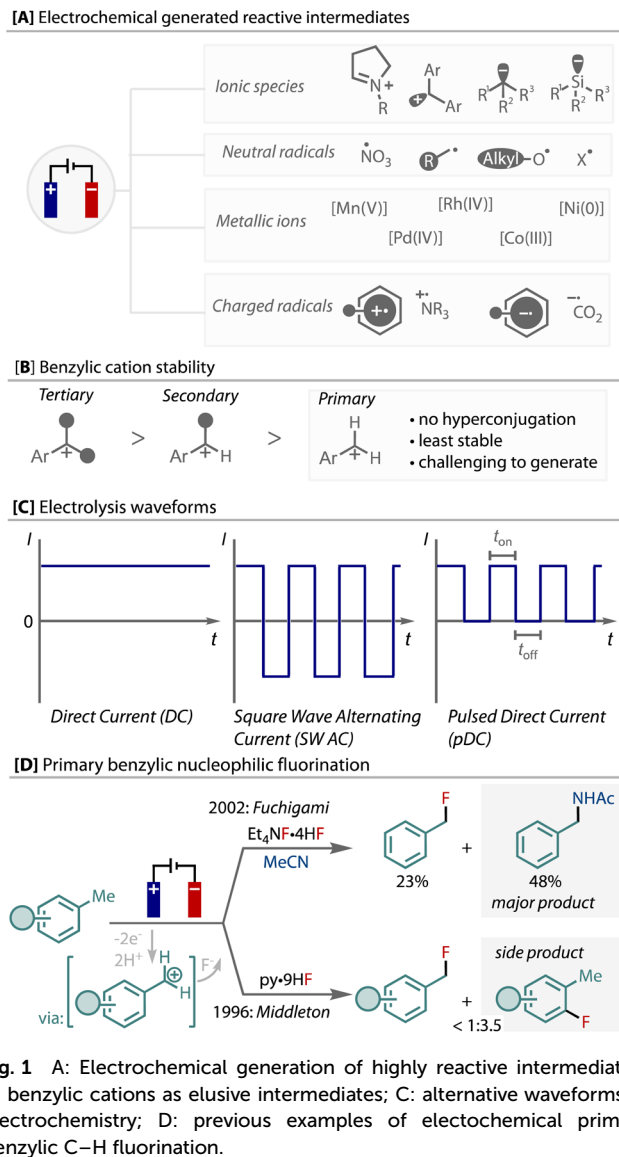


Fig. 1 A: Electrochemical generation of highly reactive intermediates; B: benzylic cations as elusive intermediates; C: alternative waveforms in electrochemistry; D: previous examples of electrochemical primary benzylic C–H fluorination.

toluene derivatives. In addition, unlike secondary and tertiary benzylic fluorides,^{52,61,63} most primary benzyl fluorides are stable and can be isolated. Herein, we describe our studies on this reaction, in which we have discovered that the unusual action of either pulsing direct current (pDC) or pulsed step constant potential (pSCP) is able to achieve enhanced yield and selectivity in this highly challenging transformation.

Our exploration studies employed biphenyl **1a** due to its low volatility and ease of monitoring by ¹⁹F NMR, Fig. 2. Variation of the fluoride source, equivalents, solvent, temperature and concentration afforded the corresponding benzyl fluoride **2a** in 34% yield after passing 2F and stirring at 1000 rpm, Fig. 2A. The outcome remained sensitive to the fluoride, with Et₃N·3HF identified as the best source, serving as the supporting electrolyte, fluoride source and a source of proton as the oxidant for the cathodic counter-electrode process.⁶⁴ A divided cell did not improve the yield.

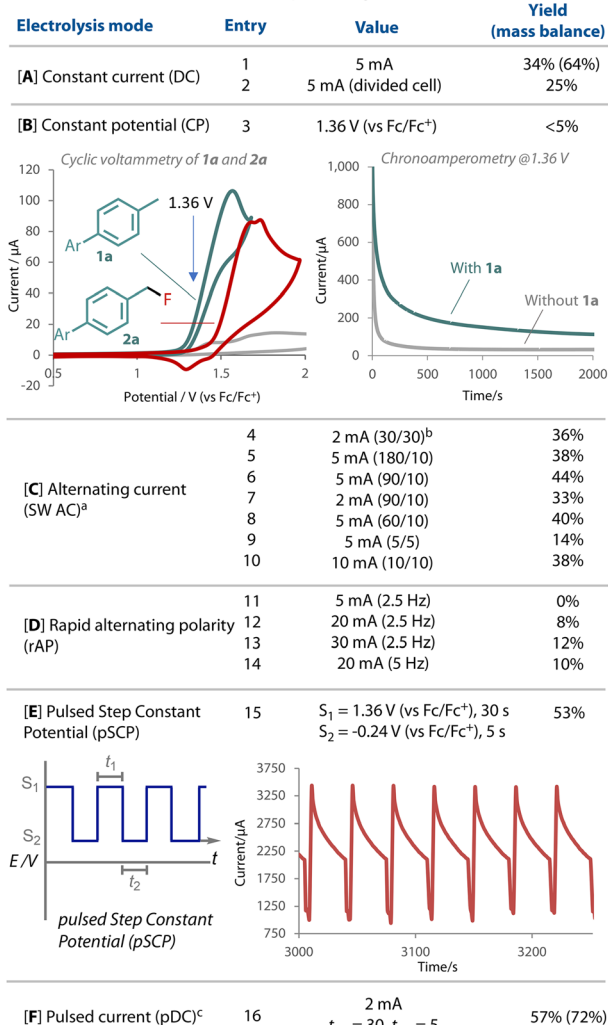
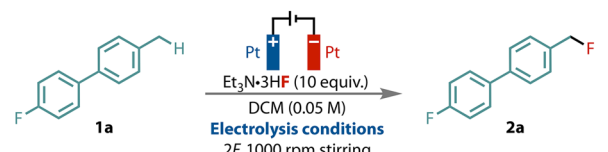


Fig. 2 Summary of electrochemical waveforms tested on the transformation of **1a** to **2a**. NMR yields. ^aSW = square wave; ^bthe square wave period sequence, seconds. ^c2,6-lutidinium.HBF₄ (0.1 M) added.

Electrode fouling and grafting were indeed observed on the anode and cathode during these preliminary studies,⁴ resulting in a reduced mass balance of 64% with DC. Unsuccessful attempts to characterise discrete surface species support substrate decomposition through over-oxidation. As the difference in the onset potential between substrate **1a** and product **2a** is



small, Fig. 2B, we elected to apply a constant potential of 1.36 V (vs. Fc/Fc⁺), which is specific for **1a** oxidation but below the onset of product **2a**. Surprisingly however, although the current response was initially at levels expected for the concentration and electrode surface area, it rapidly dropped off to the μ A range, even with rapid stirring, and resulted in only trace **2a**, Fig. 2B. The observed current was only marginally greater than the non-faradaic background current observed when no **1a** was present. This effect may be due to the formation of an insulating film,^{21,65} possibly from electrode polarisation, which limits access of substrate **2a** to the electrode surface.

The use of a square wave alternating current (AC) was tested by switching the polarity between the two electrodes and holding for a certain length of time, Fig. 2C. Several different period-lengths were tested,⁶⁴ and a 10% yield improvement was observed compared to direct current. We also tested rapid alternating current (rAP), Fig. 2D, following several recent successful examples that have led to unique selectivity.^{28–30} However, unfortunately, with all the currents and frequencies that we applied, lower yields were observed in all cases.

Interestingly, significant improvement was observed when a pulsed step constant potential (pSCP) electrolysis was performed, in which two levels of constant potential were cycled ($S_1 = 1.36$ V $t_1 = 30$ s, $S_2 = -0.24$ V $t_2 = 5$ s), Fig. 2E. This method afforded the greatest improvement in yield, entry 15. This result was especially curious considering that when 1.36 V was run continuously only trace product was observed (entry 3). This waveform has been shown to improve reactant mass transport and concentrations at the working electrode in reductive acrylonitrile dimerization,⁶⁶ and has also been reported previously in CO₂ reductive electrolysis.⁶⁷ The introduction of a second step potential serves as a resting potential, which limits faradaic processes.

Analysis of the chronoamperometry output during the step potential experiment showed high currents at the start of each S_1 period. The current decreased during this period, before rapidly decreasing during the resting, S_2 , period when lower potential is applied, Fig. 2E. The next S_1 period restores the higher level of observed current, and the cycle repeats. What is most significant to note here is that compared to the constant potential (chronoamperometry) experiment, inclusion of the resting, S_2 , period induces substantially higher currents, both at the peak and also throughout the S_1 period (Fig. 2E vs. B). The sharp reduction in observed current during S_2 suggests periods of suppressed faradaic reactivity are occurring and facilitating the improvement in reactivity. This further highlights the fragility of the relationship between electrical double layer and reaction outcome.

A mean average of 2 mA was observed during the step electrolysis reaction, therefore for practicality purposes we elected to use a pulsed direct current electrolysis (pDC) ($t_{on} I = 2$ mA; $t_{off} I = 0$ mA) as a means of cycling through productive and resting cycles. Several different t_{on} and t_{off} period lengths were tested, Fig. 2F, where it was found that pulsing at 2 mA for 30 seconds (t_{on}) followed by a 5 seconds period where no current

was applied (t_{off}) yielded reliably enhanced yields of the primary benzylic fluorination product, entry 16.

Analysis of the different pulsing sequences tested with pDC, Fig. 2F, showed that, while the inclusion of a t_{off} period clearly improved the reaction outcome, adjustment of its duration did not have a significant impact, as demonstrated by the flat line of best fit, Fig. 2F (orange line). With regards to the t_{on} period, 30 seconds proved to be optimal, with longer and shorter periods showing a decline in the yield of **2a** (blue points).

We sought to validate the difference between pDC and DC by applying the two different waveforms across a selection of other primary benzylic substrates and monitoring the yield, Fig. 3. To provide the greatest confidence in the results, we per-

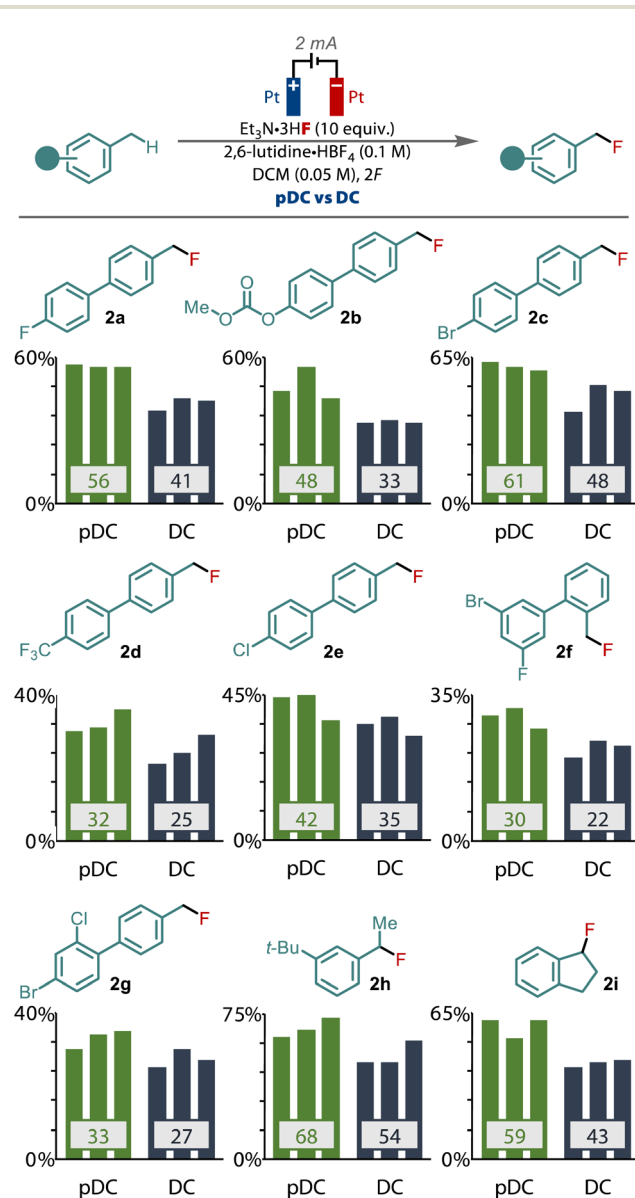


Fig. 3 Comparison of pDC vs. DC electrolysis for a selection of primary and secondary benzylic substrates.



formed each reaction in triplicate to verify the improvement that pulsed current electrolysis provides. These studies revealed that an enhanced yield was observed when applying PC compared to DC, in every substrate tested that gave synthetically useful yields. For example, for model substrate **1a** an average enhancement of 15% was observed with PC, while other substrates (**1b–g**), including those with halide, carbonate and trifluoromethyl substituents gave equally significant improvements to the yield for these primary benzylic fluorides. Only in low yielding substrates (<20%) was there no significant difference between PC and DC observed. Pulsed current also led to similar benefits for the fluorination of secondary benzylic substrates too, as exhibited by **1h** and **1i**, highlighting that this effect also relates to the fluorination of secondary benzylic cations.

To confirm the differences between constant potential and pulsed step constant potential electrolysis, we elected to switch between both techniques in a single reaction of **1a** to **2a**, and take aliquots to gauge the corresponding level of product formation that each waveform is responsible for, Fig. 4A. Consistent with what was observed during their exclusive use (Fig. 2E vs. B), product formation was only observed during periods where step potential was applied and the reaction completely stalled when constant potential was applied. Interestingly, the consumption of **1a** still occurred, albeit in an attenuated rate, during the periods of constant potential, demonstrating the sensitive nature of the intermediates formed. To the best of our knowledge, this remarkable effect has not been previously reported, and clearly demonstrates the importance of controlling the electrode/solution interface.

Despite rapid stirring in all experiments presented thus far, we proposed this effect to be due to limitations of mass transport within a highly ordered fluoride-containing electrical double-layer. Pulsed and direct current were therefore compared under different stirring regimes to add insight to this hypothesis. Both the yield and mass balance are higher with pulsed current than with direct current when the reaction is stirred rapidly, Fig. 4B. However, without stirring, although the mass balance is still different, the yield of product **2a** was the same with both pulsed and direct currents. Hence, when the solution at the electrode is not replaced, pulsing has no effect compared to constant current. This evidence highlights the importance of stirring to the t_{off} period in dispersing charged species from the electrode surface and replenishing it with substrate for further reaction.

The dispersion of charged species during the t_{off} periods can be observed by measuring the cell potential during periods when no current is flowing through the cell *via* open-circuit potential (OCP) measurements before and after electrolysis, Fig. 4C. The OCP (E_{cell} , red line) remained low and constant before electrolysis. During pulsed current (pDC) electrolysis (blue line) a high E_{cell} was maintained and then dropped during t_{off} , but to a level much higher than the original OCP. The difference between the t_{on} and t_{off} periods ($E_{\text{cell}}^{\text{max-min}}$) was only *ca.* 1 V, compared to a $E_{\text{cell}}^{\text{max-OCP}}$ of almost 3 V. Despite the absence of applied current during these t_{off} periods, the

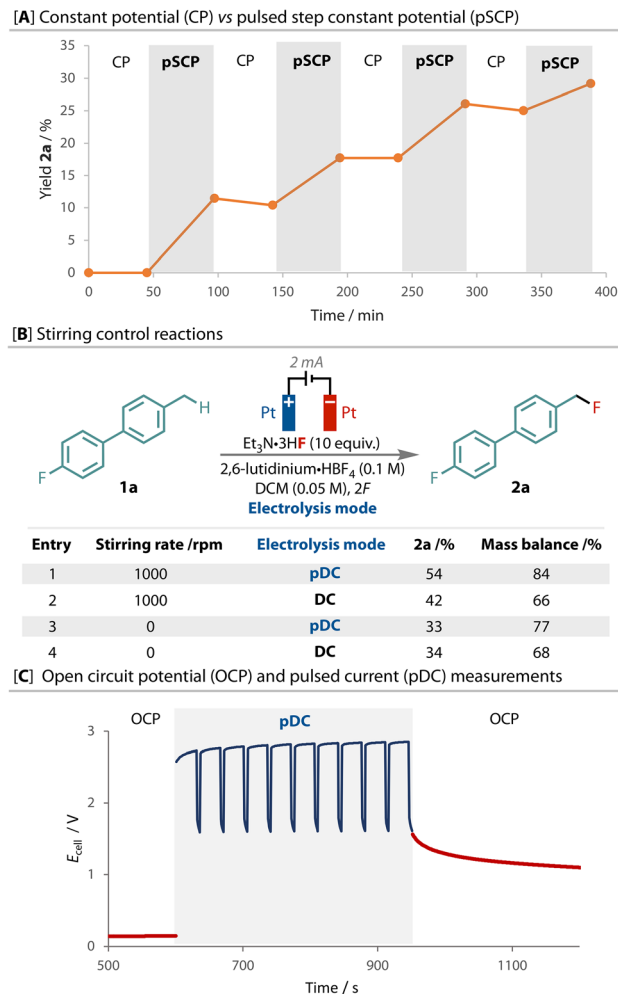


Fig. 4 A: Sequential direct and pulsed potential experiment showing how the yield of **2a** only increases during the pulsed periods, but the loss of substrate **1a** occurs under both regimes, albeit faster in pulsed. B: The effect of stirring on the direct and pulsed potential regimes; C: measurement of the open circuit potential before and after PP electrolysis.

observed E_{cell} does not return to pre-electrolysis levels indicating electrical activity through the delayed dispersion of charged species. This point is emphasised after electrolysis, as the OCP follows the final t_{off} period and only slowly trends toward the original OCP.

These combined results suggest that the pulse sequence, specifically the t_{off} period, is important to improve mass transport limitations through the fluorinated electrical double-layer that are observed during the constant potential experiment. In effect, pulsing increases mass transport and hence the concentration of substrate at the electrode surface,⁶⁸ but also decreases the degree of over-oxidation and decomposition.

In conclusion, we have demonstrated how the use of pulsed current (pDC) electrolysis can provide enhancements in yield and selectivity for the challenging primary benzylic C(sp³)-H fluorination reaction. By including a t_{off} period a direct current or constant potential experiment, we observed consistently



and reliably higher yields than the corresponding direct current electrolysis. Our analysis suggests that this approach allows for modulation of the electrical double layer to improve mass transport in this reaction, replenish substrate at the electrode surface, reduce over oxidation and decomposition and improve reaction efficiency. More broadly, this work demonstrates the increased control that is possible for the generation and functionalisation of reactive intermediates when using alternative electrolysis waveforms, and therefore should find further application in the field of synthetic organic electrosynthesis.

Conflicts of interest

There are no conflicts to declare.

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