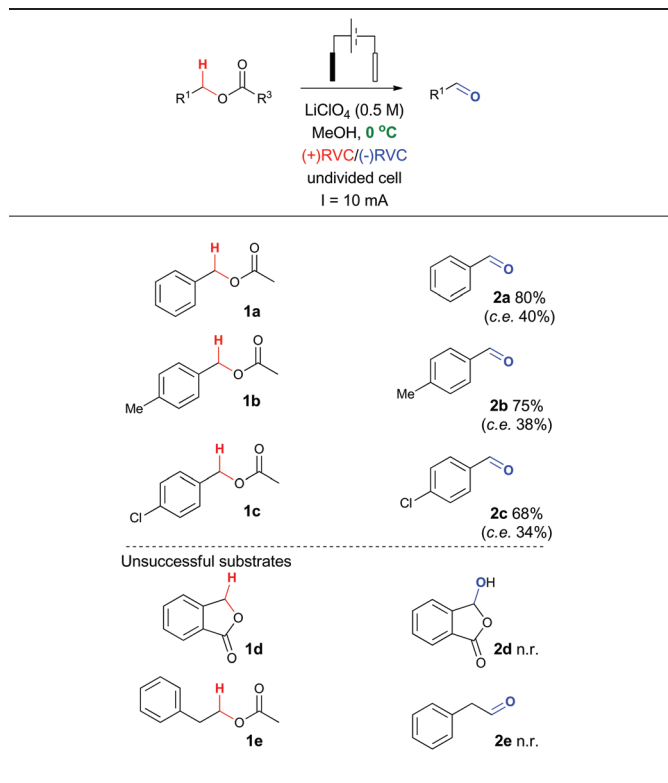


Table 2 Electro-oxidation of benzylic and homologated esters (n.r. = no reaction, c.e. = current efficiency)

afford the aldehyde **2d** and **2e**, respectively. These limitations coupled with the use of an acyl ancillary group still did not meet our green chemistry standards due to the additional

manipulation step required to prepare the acetate. We therefore considered whether a stabilising group on the heteroatom adjacent to the C–H bond was essential for successful electro-oxidation. Promisingly, cyclic voltammetry measurements on benzyl alcohol **3a** showed an oxidation wave at +1.2 V relative to Ag/AgCl.¹⁹ Using our previously optimised conditions for the ester electro-oxidation we explored the direct, mediator-free, oxidation on a range of commercially available alcohols (Table 3).

It was possible to cleanly convert benzyl alcohol (**3a**) to benzaldehyde (**2a**) under the mild conditions of lithium perchlorate in methanol in near quantitative yield and in improved yield compared to the chemical manipulation of forming the benzyl acetate (99% vs. 80%, respectively).²⁰ The scope of this reaction was further investigated *via* exploration of the effects of electron withdrawing and donating group around the ring system and steric effects around the reacting centre. The use of a chlorine atom as an electron withdrawing group in the *ortho*- (**2f**, 81%), *meta*- (**2g**, 55%) and *para*- (**2h**, 86%) positions was well tolerated. The use of a methyl group as a mild electron donating group in the *ortho*- (**2i**, 66%), *meta*- (**2j**, 99%) and *para*- (**2b**, 83%) positions also afforded good to excellent yields of the aldehyde.

Intriguingly, a strong electron donating group *para* to the reacting centre (from *para*-methoxy benzyl alcohol) resulted in a greatly reduced yield of aldehyde **2k** (27%). The relatively low yield of **2k** compared with other benzaldehydes is likely to be due to the *para*-methoxy group stabilizing the carbon-centred benzylic radical leading to further unproductive reaction pathways and oxidative decomposition of **2k**.

The result for a strongly electron withdrawing group in the 4-position of the substrate **3j** afforded only trace conversion to

Table 3 Results of direct alcohol electro-oxidation to aldehydes (c.e. = current efficiency)



Scheme 1 Proposed mechanisms for (a) benzyl alcohol and (b) benzyl acetate electro-oxidation (w/u = work-up).

the desired product as a result of the highly electron withdrawing nature of the *para*-nitro group. Based on the experimental results above and EPR literature²¹ of related systems a tentative mechanism can be proposed (Scheme 1A).

Electro-oxidation of the benzyl alcohol reveals a benzyl radical, subsequent oxidation of the hydroxyl group will deliver an aldehyde after deprotonation. Similarly, the benzylic acetate system could proceed *via* analogous initial steps to an *O*-acyloxonium species that could be trapped with water or methanol to deliver a hemiacetal or acetal species, respectively. In turn, the hemi-acetal or acetal intermediate would collapse upon work-up to deliver the aldehyde (Scheme 1B). We have shown that mild electron withdrawing and donating groups are tolerated in both systems but those that strongly donate or withdraw electrons were less compatible with direct electro-oxidation. Nitrogen containing heterocycle (**3n**) and non-benzylic substrates (**3k–3m**) gave trace conversion (<5%) to the aldehyde. However, changing the benzene ring to a thiophene was successful, affording aldehyde **2h** in quantitative yield, demonstrating the utility of the approach in other classes of heterocyclic systems.

Conclusion

The use of mediator-free, galvanostatic, direct electro-oxidation of benzylic alcohols and acetates shows scope on a range of substrates and offers an alternative and complementary approach to the preparation of valuable aldehydes. Mechanistic investigations to determine the sequence of electro-oxidation steps are now underway.

Experimental section

General methods

Reactions were carried out under nitrogen. Organic solutions were dried over MgSO_4 . Starting materials were purchased from commercial suppliers and were used without further purification. Solvents were dried over molecular sieves (3–4 Å). Flash silica chromatography was performed using Sigma-

Aldrich high-purity grade, pore size 60 Å, 200–400 mesh particle size silica gel. ^1H and ^{13}C NMR spectra were recorded on a JEOL ECS 400 NMR Spectrometer at 400 MHz or Bruker AVIII 300 or 400 MHz spectrometers. Chemical shifts (δ) are reported relative to TMS ($\delta = 0$) and/or referenced to the solvent in which they were measured. All chemical shifts (δ) are reported in parts per million, and coupling constants (J) are reported in Hertz. Low and High-resolution mass spectrometry analysis were obtained using an Agilent 6450 LC-MS/MS system. Infrared (IR) spectra were recorded on a ThermoScientific Nicolet Impact-380 ATR-FTIR spectrometer. Electro-synthesis and cyclic voltammetry were performed using a Metrohm Autolab PGSTAT100N with a 10 Amp Booster (Metrohm Autolab, UK) with an undivided electrochemical cell. Data was processed using Autolab Nova software (version 2.0). The electrode system for electro-synthesis consisted of two reticulated vitreous carbon (RVC) electrodes (supplier: ERG Aerospace; specifications: 45 pores per inch (PPI); 800 square foot per cubic foot; size 20 × 11 × 5 mm) for galvanostatic reactions plus an additional *pseudo* Ag/AgCl reference electrode for potentiostatic reactions. Please see ref. 13 for further details and images of the reaction set-up.

General procedures and safety statements

Preparation of benzyl acetates.²² A round bottom flask equipped with a magnetic stirrer was charged with the appropriate benzyl alcohol (10.0 mmol) and acetic anhydride (15.0 mmol). The reaction mixture was refluxed (85 °C) for 15 h. Upon cooling to room temperature the reaction mixture was poured into water (50 mL). The aqueous phase was extracted with ethyl acetate (30 mL × 3). The combined organic phase was washed with 1 M aq HCl (30 mL), saturated aq NaHCO_3 (30 mL), water (30 mL), brine (30 mL), and dried (MgSO_4). The solvent was evaporated under reduced pressure to afford the title compound without further purification.

Electrosynthetic oxidation reactions. A sealable electrochemical cell equipped with a magnetic stirrer was added anhydrous methanol (10 mL), lithium perchlorate (0.53 g [0.50 M]) and the alcohol (0.5 mmol [0.05 M]) or the benzyl acetate (0.5 mmol [0.05 M]) under study. Two reticulated vitreous carbon (RVC) electrodes were inserted into the solution at a distance of approximately 0.5 cm from each other and the vial sealed. The solution was cooled to 0 °C (ice-bath) and degassed with nitrogen. A fixed current (10 mA) was passed through the solution in an ice bath until the desired charge (Q) was transferred (on average $t = 5.5$ h). Upon completion of the reaction, the solvent was evaporated (at 35 °C), the residual oil was partitioned between water (10 mL) and ethyl acetate (5 mL × 3). The combined organic extracts were dried (MgSO_4) and evaporated. Analytical quality sample of the aldehyde/ketone was obtained by column chromatography (SiO_2 ; cyclohexane–ethyl acetate) to afford the title compound.

Cyclic voltammetry studies. An undivided glass cell equipped with a rectangular reticulated vitreous carbon (RVC) anode (11 cm^2) and rectangular RVC cathode (11 cm^2), arranged opposite to one another at a distance of 3.0 mm with



a Ag/AgCl *pseudo* reference electrode placed 1.0 mm from the working electrode. To this reaction vessel was added the analyte under study (5.0 mM) in the relevant organic solvent(s) (total volume 6.0 mL) and electrolyte (e.g. tetrabutylammonium perchlorate (0.5 M)). Scan rate was varied using the Autolab Nova 2.0 software.

Caution: Perchlorates – May intensify fire. In combination with flammable solvents, all sources of ignition should be avoided. During the concentration stage of the work-up, low temperature rotary evaporation with a suitable shield should be employed. The aqueous layer (after extraction) was treated with excess sodium sulphite prior to disposal.

Caution: Passing an electrical current through flammable organic solvent – The potentiostat and wiring should be regularly inspected for faults and pass all relevant electrical tests prior to use.

Spectroscopic data

Benzyl acetate (1a).²³ The title compound was afforded as a clear oil (0.85 g, 56%) using general procedure A. ¹H NMR (400 MHz, CDCl₃) δ 7.42–7.29 (m, 5H), 5.12 (s, 2H), 2.11 (s, 3H) ppm; ¹³C NMR (100.1 MHz, CDCl₃) δ 171.0, 136.0, 128.7, 128.4, 128.3, 66.4, 21.1 ppm; *m/z* (ESI) = 151 [M + H]⁺. Spectroscopic data are in accordance with literature.

4-Methylbenzyl acetate (1b).²⁴ The title compound was afforded as a clear oil (0.78 g, 48%) using general procedure A. ¹H NMR (400 MHz, CDCl₃) δ 7.34–7.23 (m, 2H), 7.23–7.10 (m, 2H), 5.07 (s, 2H), 2.36 (s, 3H), 2.08 (s, 3H) ppm; ¹³C NMR (100.1 MHz, CDCl₃) δ 171.1, 138.2, 133.0, 129.3, 128.5, 66.4, 21.3, 21.2 ppm; *m/z* (ESI) = 165 [M + H]⁺. Spectroscopic data are in accordance with literature.

4-Chlorobenzyl acetate (1c).²⁵ The title compound was afforded as a clear oil (0.98 g, 53%) using general procedure A. ¹H NMR (400 MHz, CDCl₃) δ 7.34–7.30 (m, 2H), 7.30–7.25 (m, 2H), 5.05 (s, 2H), 2.08 (s, 3H) ppm; ¹³C NMR (100.1 MHz, CDCl₃) δ 170.9, 134.5, 134.2, 129.7, 128.8, 65.6, 21.1 ppm; *m/z* (ESI) = 185 [M³⁵Cl + H]⁺, 187 [M³⁷Cl + H]⁺. Spectroscopic data are in accordance with literature.

Phenylethyl acetate (1e).²⁶ The title compound was afforded as a clear oil (0.58 g, 36%) using general procedure A. ¹H NMR (400 MHz, CDCl₃) δ 7.34–7.19 (m, 5 H), 4.27 (t, *J* = 7.0 Hz, 2H), 2.99–2.83 (t, *J* = 7.0 Hz, 2H), 2.03 (s, 3 H) ppm; *m/z* (ESI) = 165 [M + H]⁺. Spectroscopic data are in accordance with literature.

Benzaldehyde (2a).²⁷ The title compound was afforded as a colourless oil (52 mg, 99%) using general procedure B (from benzyl alcohol, 3a). Alternatively, the title compound (42 mg, 80%) was prepared using general procedure B (from benzyl acetate, 1a). ¹H NMR (300 MHz, CD₃OD) δ 10.01 (s, 1H), 7.91–7.85 (m, 2H), 7.68–7.63 (m, 1H), 7.60–7.45 (m, 2H) ppm; ¹³C NMR (100.1 MHz, CD₃OD) δ 192.6, 136.4, 134.6, 129.9, 129.1 ppm; *m/z* (ESI) 106 [M]⁺. Spectroscopic data are in accordance with literature.

4-Methylbenzaldehyde (2b).²⁸ The title compound was afforded as a colourless oil (50 mg, 83%) using general procedure B (from 4-methylbenzyl alcohol, 3b). Alternatively, the title compound (90 mg, 75%) was prepared using general pro-

cedure B (from 4-methylbenzyl acetate, 1b). ¹H NMR (300 MHz, CD₃OD) δ 9.95 (s, 1H), 7.77 (d, *J* = 8.0 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 2.43 (s, 3H) ppm; ¹³C NMR (100.1 MHz, CD₃OD) δ 191.9, 145.5, 134.2, 129.8, 129.7, 21.7 ppm; *m/z* (ESI) 121 [M + H]⁺. Spectroscopic data are in accordance with literature.

4-Chlorobenzaldehyde (2c).²⁸ The title compound was afforded as a white powder (60 mg, 86%) using general procedure B (from 4-chlorobenzyl alcohol, 3c). Alternatively, the title compound (48 mg, 68%) was prepared using general procedure A (from 4-chlorobenzyl acetate, 1c). ¹H NMR (300 MHz, CDCl₃) δ 10.00 (s, 1H), 7.94–7.78 (m, 2H), 7.71–7.43 (m, 2H) ppm; ¹³C NMR (100.1 MHz, CDCl₃) δ 190.1, 140.7, 134.5, 130.1, 129.2 ppm; *m/z* (ESI) 139 [M – H]⁺. Spectroscopic data are in accordance with literature.

2-Chlorobenzaldehyde (2f).²⁸ The title compound was afforded as a colourless oil (57 mg, 81%) using general procedure B (from 2-chlorobenzyl alcohol, 3d). ¹H NMR (300 MHz, CDCl₃) δ 10.48 (s, 1H), 7.92–7.89 (m, 1H), 7.56–7.50 (m, 1H), 7.49–7.42 (m, 2H) ppm; ¹³C NMR (100.1 MHz, CDCl₃) δ ppm 190.0, 138.2, 135.2, 132.5, 130.7, 129.5, 127.4 ppm; *m/z* (ESI) 139 [M – H]⁺; Hi-Res LC-MS (ESI) *m/z* calcd for C₇H₅OCl [M – H]⁺ 138.9956, found 138.9961. Spectroscopic data are in accordance with literature.

3-Chlorobenzaldehyde (2g).²⁸ The title compound was afforded as a colourless oil (39 mg, 55%) using general procedure B (from 3-chlorobenzyl alcohol). ¹H NMR (300 MHz, CDCl₃) δ 9.97 (s, 1H) 7.89–7.83 (m, 1H) 7.79–7.73 (m, 1H) 7.51–7.45 (m, 2H) ppm; ¹³C NMR (100.1 MHz, CDCl₃) δ 190.8, 137.8, 135.4, 134.5, 130.5, 129.4, 127.8 ppm; *m/z* (ESI) 139 [M – H]⁺. Spectroscopic data are in accordance with literature.

Thiophene-2-carbaldehyde (2h).²⁹ The title compound was afforded as a pale yellow oil (55 mg, 99%) using general procedure B (from 2-thiophenemethanol). ¹H NMR (400 MHz, CDCl₃) δ 9.95 (d, *J* = 1.3 Hz, 1H), 7.78 (ddd, *J* = 5.0, 3.8, 1.2 Hz, 2H), 7.22 (dd, *J* = 5.0, 3.8 Hz, 1H) ppm; ¹³C NMR (100.1 MHz, CDCl₃) δ 183.0, 144.0, 136.3, 135.1, 128.3 ppm; *m/z* (ESI) 111 [M – H]⁺. Spectroscopic data are in accordance with literature.

2-Methylbenzaldehyde (2i).²⁷ The title compound was afforded as a colourless oil (39 mg, 65%) using general procedure B (from 2-methylbenzyl alcohol). ¹H NMR (300 MHz, CDCl₃) δ 10.29 (s, 1H), 7.82 (d, *J* = 7.3 Hz, 1H), 7.51–7.31 (m, 3H), 2.69 (s, 3H) ppm; ¹³C NMR (100.1 MHz, CDCl₃) δ 192.7, 140.2, 133.9, 133.5, 131.9, 131.5, 126.1, 20.1 ppm; *m/z* (ESI) 121 [M + H]⁺; Hi-Res LC-MS (ESI) *m/z* calcd for C₈H₈O [M + H]⁺ 121.0648, found 121.0644. Spectroscopic data are in accordance with literature.

3-Methylbenzaldehyde (2j).³⁰ The title compound was afforded as a clear oil (59 mg, 99%) using general procedure B (from 3-methylbenzyl alcohol). ¹H NMR (300 MHz, CDCl₃) δ 9.98 (s, 1H), 7.77–7.58 (m, 2H) 7.48–7.38 (m, 2H), 2.43 (s, 3H) ppm; ¹³C NMR (100.1 MHz, CDCl₃) δ 192.8, 138.4, 136.5, 135.4, 130.1, 129.0, 127.3, 21.5 ppm; *m/z* (ESI) 121 [M + H]⁺. Spectroscopic data are in accordance with literature.

4-Methoxybenzaldehyde (2k).²⁷ The title compound was afforded as a colourless oil (18 mg, 27%) using general pro-



cedure B (from 4-methoxybenzyl alcohol). ^1H NMR (300 MHz, CDCl_3) δ ppm 9.88 (s, 1H) 7.88–7.78 (m, 2H) 7.09–6.95 (m, 2H) 3.89 (s, 3H); ^{13}C NMR (100.1 MHz, CDCl_3) δ 190.4, 164.3, 131.5, 129.8, 113.9, 55.6 ppm; m/z (ESI) 135 $[\text{M} - \text{H}]^+$; Hi-Res LC-MS (ESI) m/z calcd for $\text{C}_8\text{H}_8\text{O}_2$ $[\text{M} - \text{H}]^+$; 135.0452, found 135.0454. Spectroscopic data are in accordance with literature.

Conflicts of interest

There are no conflicts to declare.

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