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# Direct electrochemical synthesis of pentafluorophenyl esters *via* oxyl-radical-promoted nucleophilic aromatic substitution†

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An electrochemical coupling between carboxylic acids and pentafluorophenol (PFP–OH) to access synthetically versatile pentafluorophenyl (PFP) esters has been developed. Novel reactivity of PFP–OH was turned on by modulating its oxidation state, leveraging both its native *O*-nucleophilicity and its latent, oxidation-induced *C*-electrophilicity to promote a unique cascade of nucleophilic aromatic and acyl substitutions. Its esterification with acids was thus achieved for the first time without exogenous dehydrating agents. The acidity of PFP–OH and the oxidizability of its conjugate base enabled its mild and selective activation *via* deprotonation–oxidation, readily affording PFP esters that are useful in many applications (peptide synthesis, chemical biology, *etc.*) and that contain redox-sensitive functional groups. Finally, we verified in a unified forum that an amino-acid-derived PFP ester can be converted into a range of acyl-substitution products while retaining key stereochemical information, and we demonstrated that PFP esters have excellent stability to hydrolysis, comparing favorably even to *N*-hydroxysuccinimidyl (NHS) esters.

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## Introduction

Nucleophilic acyl substitutions are indispensable synthetic transformations, providing access to a range of products such as amides, esters, thioesters, ketones, aldehydes, and other useful compounds.<sup>1–4</sup> Since their development over 50 years ago, pentafluorophenyl (PFP) esters have emerged as leading forms of ‘active esters’<sup>5–9</sup> designed to undergo these reactions. These acyl electrophiles contain good leaving groups (conjugate acid  $pK_a = 4–10$  in  $H_2O$ )<sup>10–12</sup> and thus react well with a broad range of nucleophiles to afford the corresponding acid-substitution products while requiring only a mild base to achieve high yields. Further notable classes of active esters include *N*-hydroxysuccinimidyl (NHS), *N*-hydroxybenzotriazolyl, and nitrophenyl esters, among others. Owing the empowering reactivity of PFP esters with nucleophiles, as well as their bench- and water stability (which is superior to that of NHS esters<sup>13–15</sup> that are used for similar applications; see below), they have found use in a

range of applications, including the synthesis of peptides,<sup>16–20</sup> glycosides,<sup>21,22</sup> materials,<sup>23–31</sup> and pharmaceuticals,<sup>32–36</sup> as chemical biology reagents,<sup>37–45</sup> and for new synthetic methods<sup>46–55</sup> (Fig. 1a).

PFP esters have exclusively been prepared, however, from the corresponding acids (**2**) and pentafluorophenol (PFP–OH, **3**) using exogenous electrophilic dehydrating agents (Fig. 1b, left),<sup>16–50,56–58,59–79</sup> and the native electrophilicity of the latter additives gives rise to operational hazards beyond those associated with essential starting materials **2** and **3**. For instance, more-reactive variants that convert acids into acyl chlorides, such as  $SOCl_2$  and oxalyl chloride, are corrosive and acutely poisonous,<sup>80,81</sup> and milder variants for direct coupling, like carbodiimides (DCC, EDC, *etc.*), are also toxins and dermal sensitizers.<sup>82–87</sup>

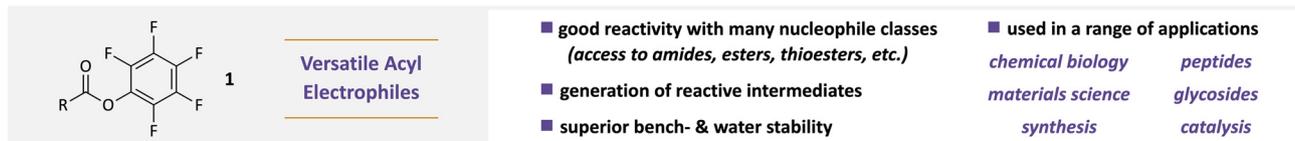
Cognizant of these challenges, we have developed a dehydrative electrochemical<sup>88–94</sup> coupling of carboxylic acids with pentafluorophenol (**3**) to afford the corresponding PFP esters (**1**). No reactive electrophiles must be added or handled since they are all anodically generated *in situ* from PFP–OH (**3**), which must already be used for PFP ester synthesis (Fig. 1b, right). The only necessary additives (base, electrolyte, and solvent) are comparatively innocuous. As detailed below, this approach electrochemically modulates the oxidation state of PFP–OH to turn on otherwise-elusive reactivity. Moreover, the facile deprotonation of this reagent and subsequent oxidation

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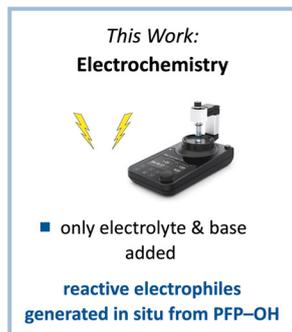
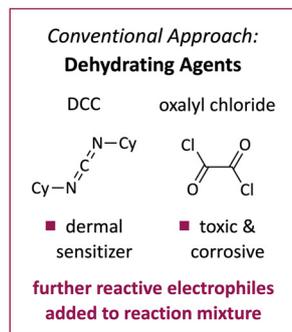
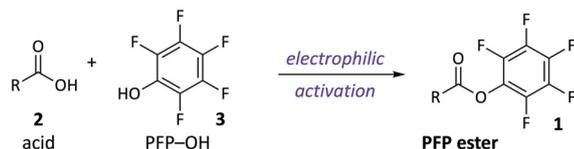
† Electronic supplementary information (ESI) available: Detailed experimental procedures, electrochemical characterization data, copies of NMR spectra and copies of HPLC for stereochemical determinations. See DOI: <https://doi.org/10.1039/d5ob00798d>



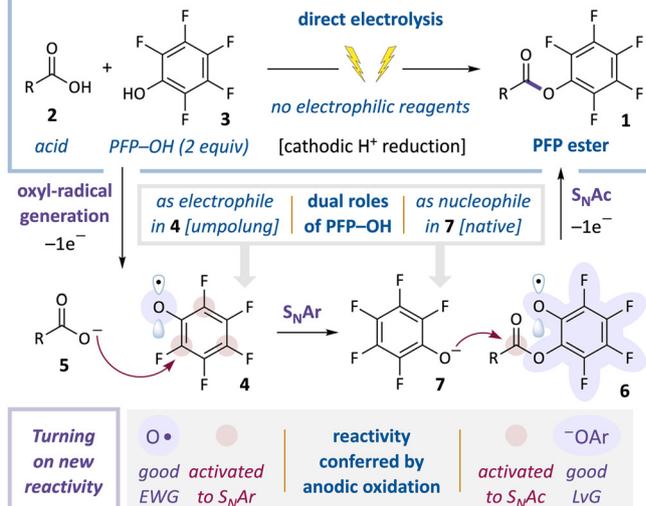
## (a) Pentafluorophenyl (PFP) Esters



## (b) Preparation of PFP Esters



## (c) Electrochemical Reaction Design



**Fig. 1** (a) Pentafluorophenyl (PFP) esters are versatile acyl electrophiles that have been used in a range of applications. (b) PFP esters are conventionally prepared using electrophilic dehydrating agents. This work avoids the handling of reactive electrophiles since they are electrochemically generated *in situ* from PFP-OH, which must be used anyway to access the desired products. (c) Our reaction design involves the anodic activation of PFP-OH (3) as the corresponding oxyl radical (4), which activates F atoms to nucleophilic aromatic substitution by acid 2 (as its conjugate base, 5). Subsequently, resulting intermediate 6 acylates a second equivalent of PFP-OH (as its conjugate base, 7) to generate the desired PFP ester (1).

of its conjugate base lead to mild conditions and an excellent scope for this new electrochemical method.

and (2) as a native nucleophile for S<sub>N</sub>Ac, which forms the product.

## Design plan

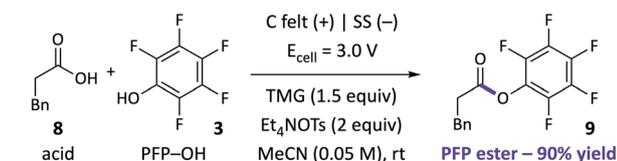
Our reaction design (Fig. 1c) is initiated by deprotonation and single-electron anodic oxidation of PFP-OH (3, pK<sub>a</sub> = 20.1 for PFP-OH<sup>95</sup> and E<sub>p</sub><sup>ox</sup> = +0.27 V vs. SCE for PFPO<sup>-</sup>, both in MeCN) to generate oxyl radical 4. The *ortho*- and *para*-C-F groups of this intermediate are activated (red shading on C) to otherwise-challenging nucleophilic aromatic substitution (S<sub>N</sub>Ar) by carboxylate ion 5, owing to the exceptional electron-withdrawing character<sup>96</sup> of the conjugated oxyl radical (purple shading) that has an underfilled octet. The resulting, putative *O*-aryl ester 6 (or a redox analog thereof) would then contain a good phenoxide leaving group (purple shading), making it susceptible to nucleophilic acyl substitution (S<sub>N</sub>Ac, red shading on C) by PFP-O<sup>-</sup> (7). This step would afford desired PFP ester 1 and a quinone-type byproduct (not shown) after another anodic oxidation. The electrical circuit would be closed by cathodic proton reduction. Overall, this design uses the PFP-OH hydroxyl group in two ways: (1) as a latent umpolung electrophile, leading to the S<sub>N</sub>Ar that activates the carboxylic acid,

## Results

Starting from this conceptual basis, we identified a simple protocol that efficiently converted model acid 8 and PFP-OH (3) into PFP ester 9 (Fig. 2, see scheme). Under optimized conditions, a mixture of 8 and 3, an organic base (N<sup>1</sup>,N<sup>1</sup>,N<sup>2</sup>,N<sup>2</sup>-tetramethylguanidine, TMG, 1.5 equiv.), and an electrolyte (Et<sub>4</sub>NOTs, 2 equiv.) in MeCN (0.05 M in 8) was electrolyzed at a constant cell potential of 3.0 V between a carbon-felt anode and a stainless-steel cathode in an undivided cell, affording PFP ester 9 in 90% yield. Optimal yields of 9 were obtained with a fivefold excess of PFP-OH, but similar or better yields were often obtained with a more-modest excess (3 equiv. of PFP-OH and 1 equiv. of TMG, see below and ESI†).

The impact of key reaction parameters is also shown in Fig. 2. Carbon anodes proved uniquely effective, and a lower-porosity material (graphite) was less efficient than C felt (58% yield, entry 1a). Replacing the stainless-steel cathode with C felt was counterproductive (34% yield, entry 1b). Only Pt proved comparable (87% yield, entry 1c), but it was not used





parameter entry	change a yield (%)	change b yield (%)	change c yield (%)	change d yield (%)	change e yield (%)
<b>electrodes</b>	<b>graphite (+)</b>	<b>C felt (-)</b>	<b>Pt (-)</b>	–	–
entry 1	58	34	87	–	–
<b>electrolyte</b>	<b>Bu<sub>4</sub>NPF<sub>6</sub></b>	<b>Et<sub>4</sub>NPF<sub>6</sub></b>	<b>Et<sub>4</sub>NBF<sub>4</sub></b>	<b>Et<sub>4</sub>NCl</b>	<b>Me<sub>4</sub>NOH</b>
entry 2	53	64	59	80	80 (no TMG)
<b>eChem</b>	<b>E<sub>cell</sub> = 2.5 V</b>	<b>E<sub>cell</sub> = 3.5 V</b>	<b>I = 15 mA</b>	<b>I = 25 mA</b>	–
entry 3	30	77	88	32	–
<b>solvent</b>	<b>DMF</b>	<b>DMSO</b>	<b>+5 eq H<sub>2</sub>O</b>	<b>+10 eq H<sub>2</sub>O</b>	–
entry 4	67	10	75	66	–
<b>base</b>	<b>Et<sub>3</sub>N</b>	<b>DBU</b>	<b>Na<sub>2</sub>CO<sub>3</sub></b>	<b>Na<sub>3</sub>PO<sub>4</sub></b>	<b>NaOH</b>
entry 5	89	55	15	20	9
<b>[PF<sub>6</sub>OH]</b>	<b>1 eq</b>	<b>2 eq</b>	<b>3 eq</b>	<b>4 eq</b>	<b>6 eq</b>
entry 6	2	15	77	83	42
<b>[PF<sub>6</sub>OH]</b>	<b>1 eq</b>	<b>2 eq</b>	<b>3 eq</b>	<b>4 eq</b>	<b>5 eq</b>
7 (1 eq TMG)	3	35	87	76	69
<b>atmosphere</b>	<b>air</b>	<b>N<sub>2</sub> (no sparge)</b>	–	–	–
entry 8	0	51	–	–	–

**Fig. 2** Control experiments electrolyzed a mixture of acid **8** (0.5 mmol, 1 equiv.), PFP–OH (**3**, 5 equiv.), TMG (1.5 equiv.), and Et<sub>4</sub>NOTs (2 equiv.) in MeCN (0.05 M in **8**) at a constant cell potential of 3.0 V between a carbon-felt anode and stainless-steel cathode. Yields were determined by <sup>1</sup>H NMR analysis with an internal standard. Deviations are noted below the scheme. See ESI† for details.

thereafter owing to its much-higher cost. Tetraalkylammonium PF<sub>6</sub> and BF<sub>4</sub> electrolytes proved inferior to Et<sub>4</sub>NOTs (53–64% yields, entries 2a–c), although Et<sub>4</sub>NCl performed similarly (80% yield, entry 2d). Me<sub>4</sub>NOH could serve the dual role as electrolyte and base (80% yield without TMG, entry 2e), albeit in slightly reduced yield. Changes to the cell potential or switching to constant current gave lower yields (entries 3a–d), although a 15 mA current proved efficient (88% yield, entry 3c). The only solvent remotely comparable to MeCN was DMF (67% yield, entry 4a). DMSO (10% yield, entry 4b) represented the performance of most other solvents assessed. The process withstood appreciable amounts of water (5 & 10 equiv., giving 75% and 66% yields, respectively, entries 4c & d). The optimal base, TMG, could be exchanged for Et<sub>3</sub>N without issue in the model reaction (89% yield, entry 5a), but alternative organic bases such as DBU (55% yield, entry 5b) and especially inorganic bases, all of which were insoluble, were ineffective (9–15% yield, entries 5c–e). As mentioned above, a fivefold excess of PFP–OH (**3**) gave optimal yields when 1.5 equiv. TMG was used (compare the optimized 90% yield to entries 6a–e), but a threefold excess of PFP–OH with less TMG (1 equiv.) gave comparable results (87% yield, entry 7c). Almost all products obtained throughout this study employed one of these ratios (see below and ESI†). Finally, reaction mixtures were typically

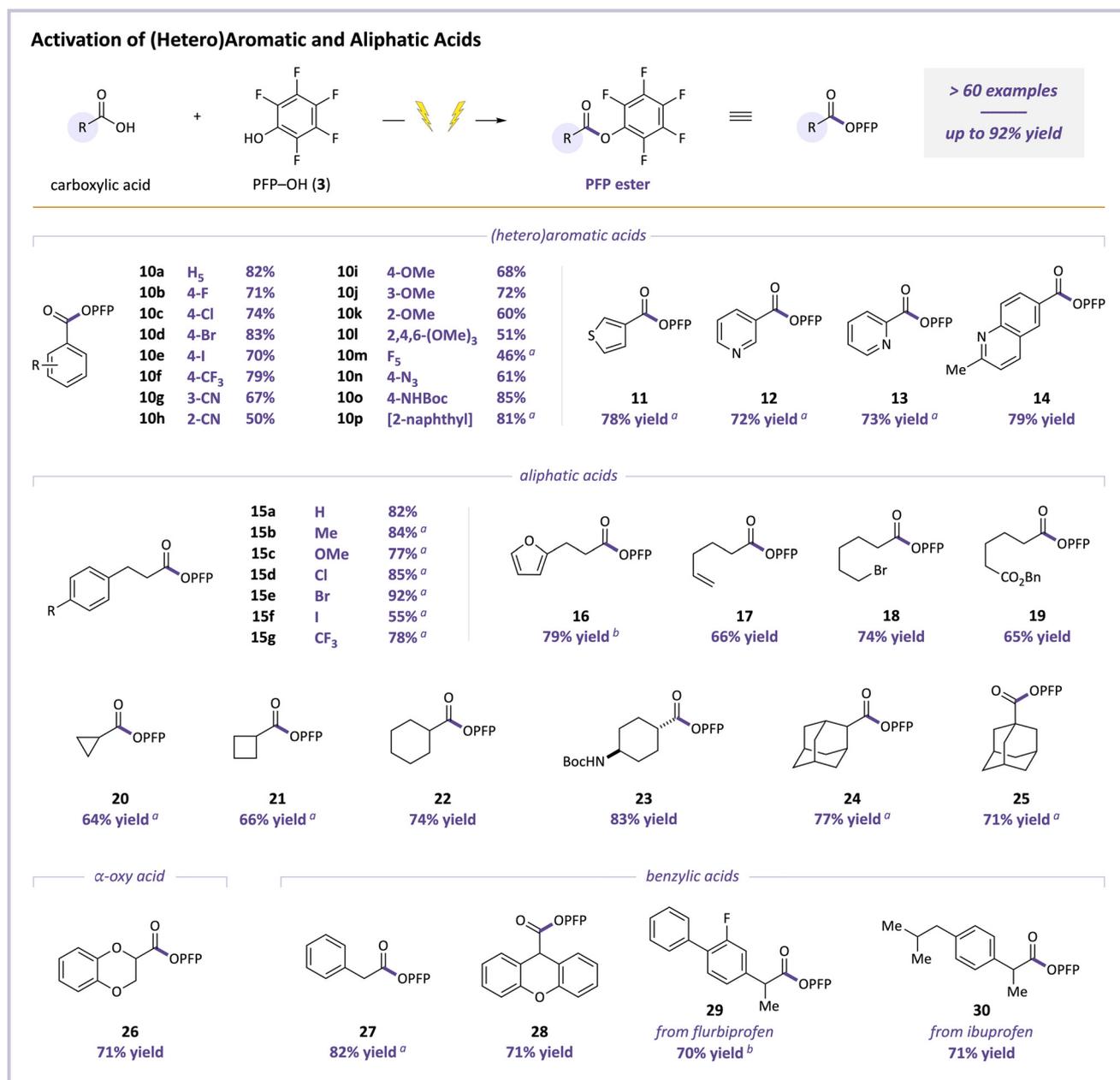
sparged with nitrogen and then electrolyzed under a nitrogen atmosphere. The reaction did not proceed under air (0% yield, entry 8a), and skipping the sparging step significantly lowered the efficiency, even if the electrolysis was performed under inert atmosphere (51% yield, entry 8b).

We then evaluated the range of carboxylic acids that could undergo this novel electrochemical PFP esterification. Functionalized aromatic and aliphatic acids were both broadly viable, as shown in Fig. 3. For example, the PFP ester of benzoic acid (**10a**) was obtained in 82% yield, and its *para*-halogenated (F, Cl, Br, and I) and CF<sub>3</sub> analogs were formed in 70–83% yields (**10b–f**). Benzoic acids with cyano and methoxy groups at different positions were competent substrates, giving products **10g–k** in 50–72% yields, as were 2,4,6-trimethoxybenzoic acid (product **10l**, 51% yield) and pentafluorobenzoic acid (product **10m**, 46% yield). PFP benzoates with nitrogen-containing *para*-azido (**10n**, 61% yield) and NHBoc (**10o**, 85% yield) groups were similarly effective. A range of extended aromatic and heteroaromatic acids were also tolerated, cleanly affording 2-naphthoic, 3-thienyl, 2- and 3-pyridyl, 6-quinolinyl PFP esters **10p** and **11–14** in 72–81% yields.

In terms of aliphatic acids, 3-phenylpropionate product **15a** was isolated in 82% yield, and its *para*-methyl, methoxy, chloro, bromo, iodo, and trifluoromethyl analogs **15b–g** were obtained in 55–92% yields (with only iodo product **15f** below 77% yield). Products containing furan, alkene, alkyl bromide, and benzyl ester groups (**16–19**, 65–79% yields) were also generated cleanly. PFP esters pendant from 3-, 4-, and 6-membered rings (**20–22**, 64–74% yields), a 4-NHBoc-substituted cyclohexane (**23**, 83% yield), and both secondary and tertiary adamantyl groups (**24** & **25**, 77% and 71% yields, respectively) were similarly prepared. Finally, an  $\alpha$ -oxy acid and a variety of benzylic acids, which are potentially sensitive to oxidative decarboxylation,<sup>97,98</sup> underwent efficient electrolysis, producing PFP esters **26–30** in 70–82% yields. The latter two examples employed the NSAIDs flurbiprofen and ibuprofen as substrates.

PFP esters derived from amino acids have proven particularly valuable as building blocks in peptide synthesis,<sup>16–20</sup> materials chemistry,<sup>23–31</sup> and chemical biology,<sup>37,38,41,42,45</sup> so we also thoroughly verified whether these products were accessible using our electrochemical system. Encouragingly, an excellent range of these PFP esters were efficiently prepared (Fig. 4). Boc-protected  $\beta$ -amino product **31** was obtained in 75% yield. The majority of our efforts then focused on  $\alpha$ -amino acids. Common Cbz, Boc, and Fmoc *N*-protecting groups were all well-tolerated on alanine, affording products **32–34** in 75–81% yields. The PFP ester of serine (**35**) bearing a free OH group was formed in 52% yield, and *O*-benzyl protection gave product **36** in higher 72% yield. With appropriate protecting groups, PFP esters of the functionalized amino acids cysteine (**37**, 52% yield), methionine (**38**, 88% yield), lysine (**39**, 74% yield), and arginine (**40**, 86% yield) were also cleanly isolated. A gram-scale preparation of arginine product **40** proceeded in nearly identical 81% yield. Functional aromatic-containing side chains were also well-tolerated, generat-





**Fig. 3** Scope for PFP esterification of (hetero)aromatic and aliphatic acids. A mixture of acid (0.5 mmol, 1 equiv.), PFP-OH (3, 3–5 equiv.), TMG (1–1.5 equiv.), and Et<sub>4</sub>NOTs (2 equiv.) in MeCN (0.05 M in acid) were electrolyzed at a constant cell potential of 3.0 V between a carbon-felt anode and stainless-steel cathode. Yields of isolated products. See ESI† for details. <sup>a</sup> Isolated as the corresponding *N*-benzylamide. <sup>b</sup> Performed on a larger scale (2 mmol of acid).

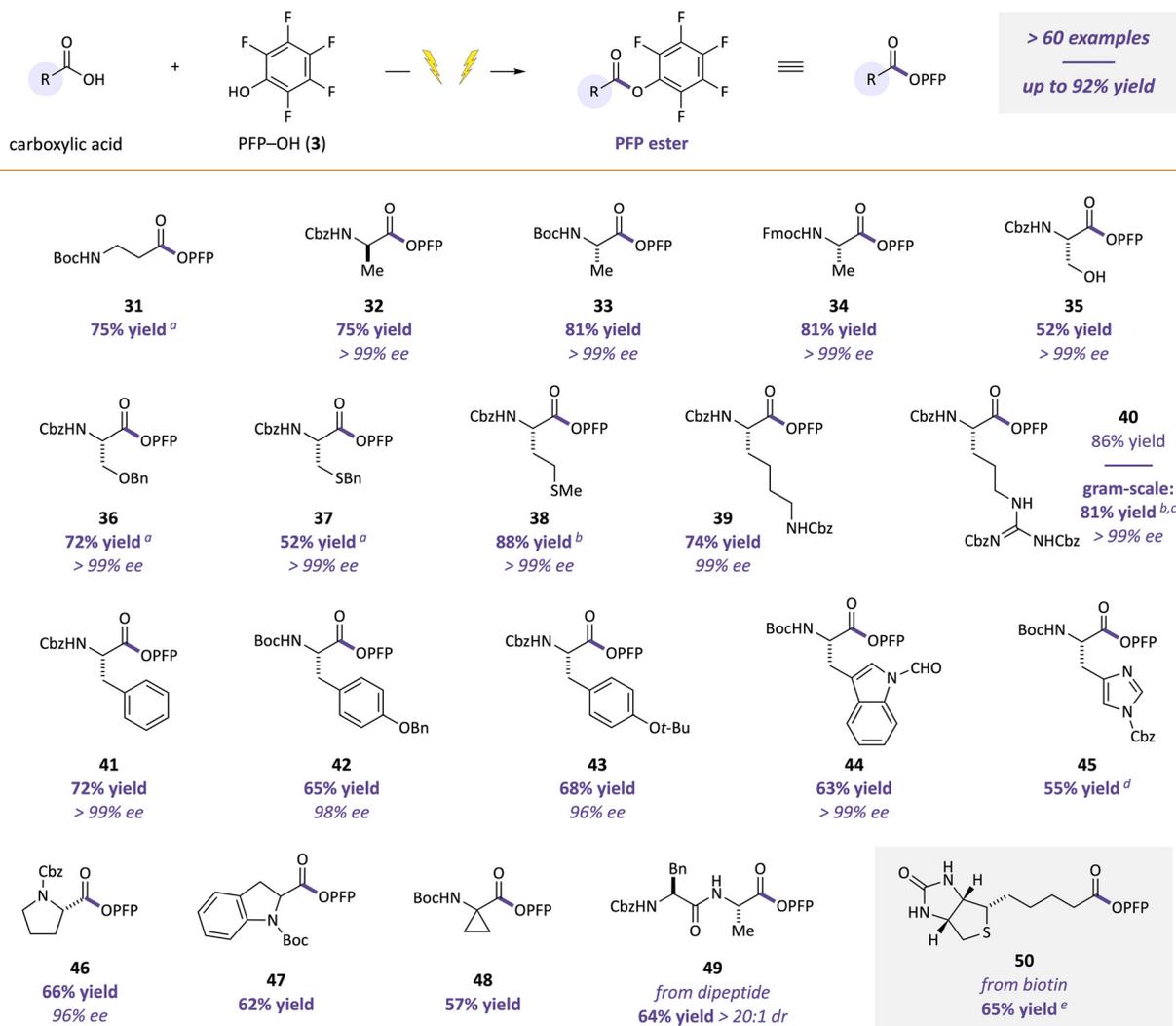
ing phenylalanine-, tyrosine-, tryptophan-, and histidine-derived products **41–45** in 55–72% yields. More-substituted  $\alpha$ -amino acids including proline and unnatural building blocks afforded products **46–48** in 57–66% yields. Critically, excellent stereoretention was observed, as all non-racemic products had  $\geq 96\%$  ee, with most  $>99\%$  ee. A dipeptide was converted to **49** (64% yield) without epimerization (20 : 1 dr), and the PFP ester of biotin (**50**), which is a useful reagent in chemical biology,<sup>39,40,43,44</sup> was isolated in 65% yield. Throughout these studies, in cases where yields of PFP esters were modest,

acid-derived byproducts were typically not observed. Instead, unproductive acid remained intact. Oligomeric PFP-OH-derived byproducts, which owing to their low polarity were readily removed by chromatography, accounted for the mass balance.

Having established the broad scope of our electrochemical PFP ester synthesis, we completed our synthetic work by confirming the well-established versatility of these products in downstream synthetic transformations (Fig. 5a). Amino-acid-derived product **41** was prepared in 72% yield (see Fig. 4) and



## Activation of Amino Acids and Biotin (for Peptide Synthesis and Chemical Biology)



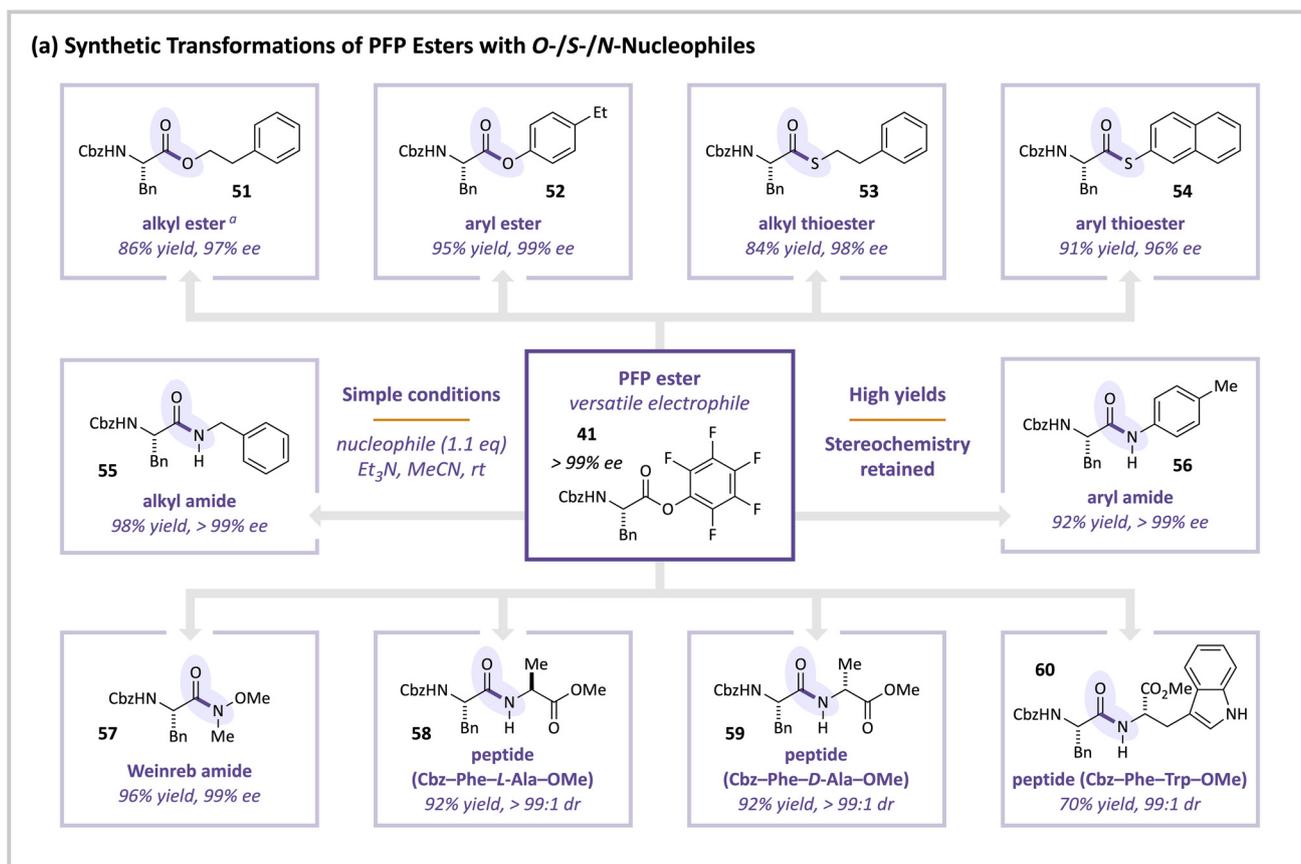
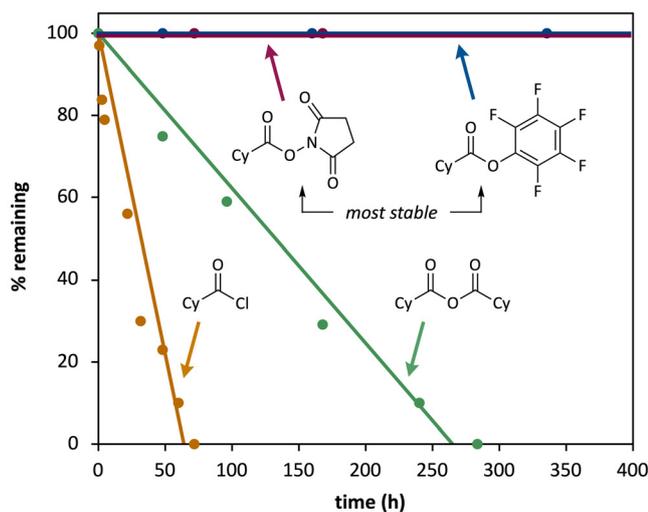
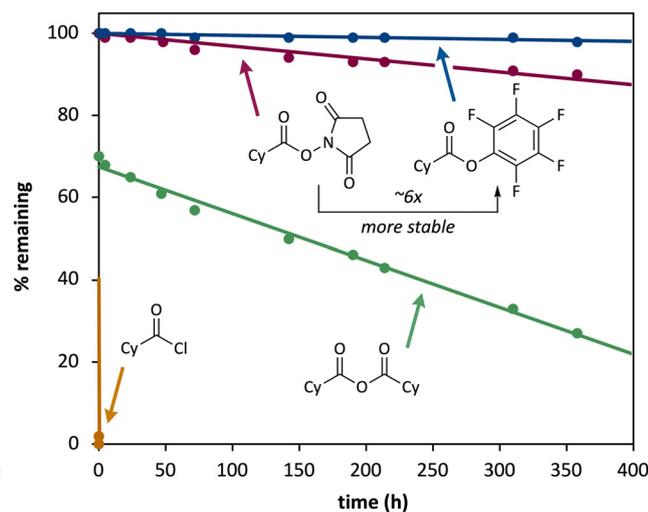
**Fig. 4** Scope for PFP esterification of amino acids and biotin. A mixture of acid (0.5 mmol, 1 equiv.), PFP-OH (**3**, 3–5 equiv.), TMG (1–1.5 equiv.), and Et<sub>3</sub>NOTs (2 equiv.) in MeCN (0.05 M in acid) were electrolyzed at a constant cell potential of 3.0 V between a carbon-felt anode and stainless-steel cathode. Yields of isolated products. See ESI† for details. <sup>a</sup> Isolated as the corresponding *N*-benzylamide. <sup>b</sup> Performed on a larger scale (2 mmol of acid). <sup>c</sup> 3.5-V cell potential. <sup>d</sup> Yield determined by <sup>19</sup>F NMR. <sup>e</sup> 3 : 1 DMF/MeCN solvent.

>99% ee. Treatment of this PFP ester with a range of nucleophiles under simple conditions (1.1 equiv. of nucleophile, 1 equiv. of Et<sub>3</sub>N, MeCN solvent) rapidly and efficiently produced the corresponding carboxylic-acid derivatives either without any or with only a minimal loss of enantiopurity. Specifically, *O*-alkyl and *O*-aryl esters **51** & **52** and *S*-alkyl and *S*-aryl thioesters **53** & **54** were isolated in 84–95% yields and 96–99% ees. *N*-Alkyl, *N*-aryl, and Weinreb amides **55**–**57** were similarly obtained in 92–98% yields and all in ≥99% ee. Lastly, using α-amino acid esters as the nucleophiles afforded dipeptides **58**–**60** in 70–92% yields and without epimerization (all ≥99 : 1 dr), which can be challenging in peptide synthesis.<sup>99–101</sup> Although these outcomes are consistent with the well-established

performance of PFP esters in a range of applications,<sup>16–55</sup> these results showcase that these electrophiles are highly effective acyl surrogates (*i.e.*, providing high yield and minimizing racemization) with a broad range of nucleophiles and without needing to re-optimize reaction conditions.

We also sought to compare the stability of amino-acid-derived PFP ester **41** to that of other acyl electrophiles, but we were unable to prepare any quantity of the acyl chloride despite reports of its synthesis.<sup>102–109</sup> We therefore compared the stabilities of the acyl chloride, anhydride, NHS ester, and PFP ester derived from cyclohexane carboxylic acid stored as neat compounds under air (Fig. 5b) and in aqueous MeCN



**(b) Stabilities of Acyl Electrophiles Stored Under Air****(c) Stabilities of Acyl Electrophiles in Aqueous Solution**

**Fig. 5** (a) Synthetic transformations of amino-acid-derived PFP ester product **36**. A range of *O*-, *S*-, and *N*-nucleophiles efficiently generated the corresponding alkyl and aryl ester, thioester, and amide products, including a selection of dipeptides, with minimal racemization. Conditions: a solution of PFP ester **36** (0.5 mmol, 1 equiv.), nucleophile (1.1 equiv.), and Et<sub>3</sub>N (1 equiv.) in MeCN (0.1 M in **36**) were stirred at rt. Yields of purified products are reported. See ESI† for details. <sup>a</sup> Performed with a larger excess of nucleophile (3 equiv.). (b & c) Stabilities of acyl electrophiles (acyl chloride, anhydride, NHS ester, and PFP ester) derived from cyclohexane carboxylic acid stored (b) under air and (c) in aqueous solution (0.1 M in 4 : 1 CD<sub>3</sub>CN/D<sub>2</sub>O), with % remaining measured by <sup>1</sup>H NMR analysis.

(Fig. 5c) by <sup>1</sup>H NMR analysis. As expected, the acid chloride decomposed much more rapidly than all other electrophiles, with a half-life of ~24 h stored under air and decomposing

completely within 72 h. The half-life of the anhydride was ~100 h under air, and it fully decomposed within 300 h, whereas neither NHS nor the PFP active esters suffered any

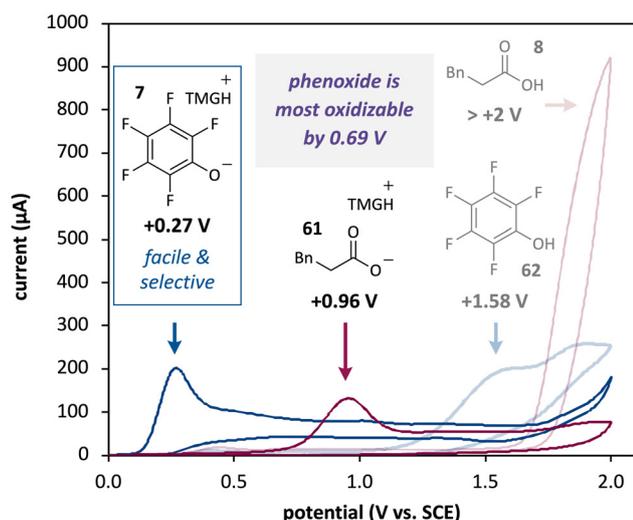


detectable decomposition after 300 h. Starker differences were observed in aqueous solution. The acyl chloride fully decomposed within 15 minutes. The anhydride had a surprisingly long half-life of ~140 h. The active esters again decomposed much more slowly, but the PFP ester remarkably proved ~6-fold more stable than the NHS ester. The combined results across Fig. 5 therefore showcase both the synthetic versatility and practical robustness of these acyl electrophiles.

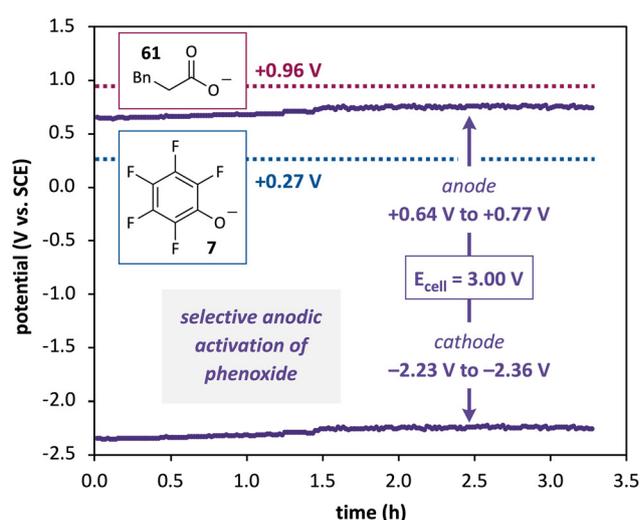
Electrochemical studies were then undertaken to account for the excellent chemoselectivity of this new electrochemical reaction. First, analysis of the reaction components by cyclic voltammetry (CV) revealed that phenoxide **7**, the anion of PFP-OH (**3**), is the most oxidizable species in solution by a significant margin (Fig. 6a). Neither PFP-OH ( $E_p^{ox} = +1.58$  V vs. SCE) nor model acid **8** ( $E_p^{ox} > +2$  V vs. SCE) were readily oxidized, which is consistent with the need for a base in the electro-

chemical reaction. The standard base employed throughout these studies (TMG,  $pK_{BH^+} = 23.4$  in MeCN,<sup>110</sup> the standard reaction solvent) can deprotonate both the carboxylic acid ( $pK_a = 23.5$  for AcOH in MeCN)<sup>95</sup> and PFP-OH ( $pK_a = 20.1$  in MeCN),<sup>95</sup> although given their relative acidities and the stoichiometries employed (either 1 : 5 : 1.5 or 1 : 3 : 1 of carboxylic acid/PFP-OH/TMG), PFP-OH should be deprotonated to a much-greater extent than the carboxylic acid (this acid-base equilibrium also makes TMG oxidation unlikely, see ESI†). Even without accounting for this speciation, which would selectively activate PFP-OH to oxidation, PFP-O<sup>-</sup> (**7**,  $E_p^{ox} = +0.27$  V vs. SCE) proved more oxidizable than the carboxylate derived from acid **8** (**61**,  $E_p^{ox} = +0.96$  V vs. SCE) by 0.69 V. We postulate that this facile oxidation underpins the generality of the synthetic protocol, which did not lead to undesired oxidation of  $\alpha$ -amino acids, benzylic acids, or dialkyl sulfides.

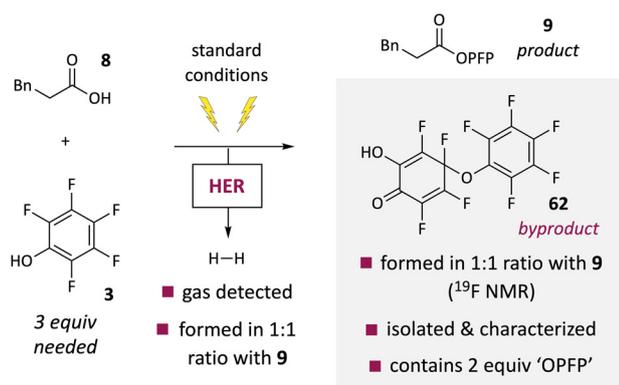
### (a) Peak Oxidation Potentials of Reactants



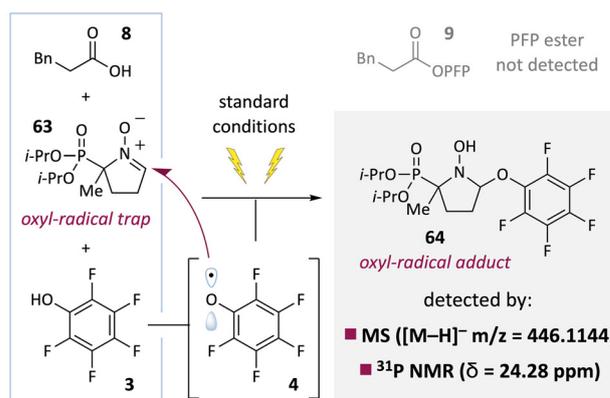
### (b) Working Potentials of Electrodes During Electrosynthesis



### (c) Detection and Characterization of Byproducts



### (d) Trapping of Oxyl-Radical Intermediate



**Fig. 6** Preliminary mechanistic experiments. (a) CV analyses revealed that the conjugate base of PFP-OH (phenoxide **7**) is oxidized at a significantly lower potential (+0.27 V vs. SCE) than any other possible major species in solution. (b) The potential of the anode varied from +0.64 V to +0.77 V vs. SCE during electrolysis, which can selectively engage phenoxide **7** while leaving carboxylates and other potentially oxidizable species intact. (c) Both H<sub>2</sub> and **62**, which contains two 'OPFP' units, were formed in equimolar ratios with PFP ester **9**. (d) The model reaction forming PFP ester **9** did not proceed when adding radical trap **63**, and oxyl-radical adduct **64** was detected by HRMS and <sup>31</sup>P NMR. See ESI† for details.



Consistent with this scenario, the potential of the anode during preparative constant-cell-potential electrolysis underwent a modest anodic drift, but it stayed within a range of +0.64 V to +0.77 V vs. SCE (Fig. 6b). Presumably, the anode selectively oxidizes the PFP-OH/PFP-O<sup>-</sup> mixture present at any given time, but never reaches an energy that would destroy the carboxylate or other groups.<sup>111</sup>

Finally, preliminary studies were performed to probe the reaction mechanism. As shown in Fig. 1c, we proposed that a net oxidation of the organic reactants would be enabled by cathodic hydrogen evolution. Indeed, preparative experiments were performed with a vent needle since the reaction vessel otherwise became noticeably pressurized and occasionally burst. A hydrogen detector confirmed the formation of this gas, and semiquantitative estimates indicated that it was produced in an equimolar amount with PFP ester **9** (Fig. 6c). Furthermore, when the reaction was monitored by <sup>19</sup>F NMR, an organic byproduct was also formed in a ~1:1 ratio with desired product **9**. Careful isolation enabled its characterization and structural assignment as **62**, which contains two 'OPFP' units. This byproduct explains why a threefold excess of PFP-OH is needed for the reaction to proceed (see Fig. 2). As discussed below, it also required a minor revision of our mechanistic hypothesis (Fig. 1c). On the other hand, the proposed single-electron oxidation to generate PFP-OH-derived

oxyl radical **4**, which would facilitate the proposed S<sub>N</sub>Ar,<sup>96</sup> was consistent with radical-trapping experiments (Fig. 6d). Addition of oxyl-radical trap **63**<sup>112</sup> to a standard preparative electrolysis completely prevented the formation of PFP ester **9**, and oxyl-radical adduct **64** was detected both by HRMS and <sup>31</sup>P NMR analysis (no adduct formation or substrate conversion of any kind occurred without electrolysis, see ESI†).

These observations led to the revised mechanistic proposal shown in Fig. 7. As initially suggested in Fig. 1c, deprotonation and single-electron anodic oxidation of PFP-OH (**3**) generate oxyl radical **4**, the highlighted C-F bonds of which are activated to S<sub>N</sub>Ar by carboxylate ion **5**.<sup>96</sup> Putative intermediate **6** then undergoes a further anodic oxidation and is trapped by a second equivalent of PFP-O<sup>-</sup> (**7**), generating closed-shell acyl electrophile **65**. Finally, S<sub>N</sub>Ac with a third and final equivalent of PFP-O<sup>-</sup> (**7**) affords PFP ester **1** and byproduct **62**.

## Conclusions

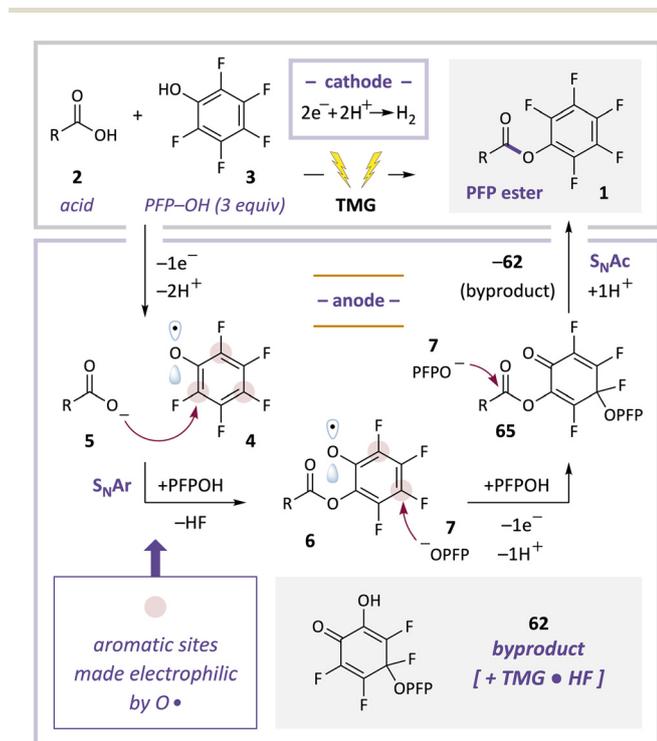
We have developed a novel electrochemical coupling of carboxylic acids with pentafluorophenol (PFP-OH) to access synthetically versatile pentafluorophenyl (PFP) esters. This system strategically modulates the oxidation state of the hydroxyl group in PFP-OH to turn on otherwise-elusive reactivity. By leveraging both the latent electrophilicity and the native nucleophilicity of this reagent, a unique S<sub>N</sub>Ar/S<sub>N</sub>Ac cascade ultimately generates the PFP ester product. As a result, this useful transformation can be accomplished for the first time without electrophilic dehydrating agents. Moreover, owing to the acid-base and electrochemical properties of PFP-OH that enabled its selective activation under mild conditions, an excellent range of PFP esters that are useful in a wide range of applications and that contain oxidation-sensitive functional groups were efficiently prepared. Finally, we confirmed that an amino-acid-derived PFP ester reliably affords a range of acyl-substitution products without any or with only minimal epimerization, and we demonstrated that PFP esters have excellent stability to hydrolysis, comparing favorably even to *N*-hydroxysuccinimidyl (NHS) esters.

## Author contributions

All authors were involved in the discovery and conception of the project. E. G. V. H., M.-C., L., and J. J. P. performed experiments and collected data. All authors analyzed data. E. D. N. prepared the manuscript and E. G. V. H. prepared the ESI.† All authors revised the manuscript.

## Data availability

Detailed experimental procedures, compound characterization data, preliminary mechanistic experiments, copies of NMR spectra (PDF).



**Fig. 7** Revised mechanistic hypothesis. Deprotonation and anodic oxidation of PFP-OH (**3**) generates oxyl radical **4**, which undergoes S<sub>N</sub>Ar with carboxylate **5**. Resulting open-shell O-aryl ester **6** is oxidized further and trapped by a second equivalent of PFP-O<sup>-</sup> (**7**), producing acyl electrophile **65**. S<sub>N</sub>Ac by a third equivalent of PFP-O<sup>-</sup> (**7**) affords PFP ester **1** and byproduct **62**.



The datasets supporting this article have been uploaded as part of the ESI.†

## Conflicts of interest

The authors declare no competing interests.

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