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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.[1–4] Since their development over 50 years ago, pentafluorophenyl (PFP) esters have emerged as leading forms of 'active esters'[5–9] designed to undergo these reactions. These acyl electrophiles contain good leaving groups (conjugate acid pK_a = 4–10 in H_2O)[10–12] 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[13–15] that are used for similar applications; see below), they have found use in a range of applications, including the synthesis of peptides,[16–20] glycosides,[21,22] materials,[23–31] and pharmaceuticals,[32–36] as chemical biology reagents,[37–45] and for new synthetic methods[46–55] (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),[16–50,56–58,59–79] 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,[80,81] and milder variants for direct coupling, like carbodiimides (DCC, EDC, *etc.*), are also toxins and dermal sensitizers.[82–87]

Cognizant of these challenges, we have developed a dehydrative electrochemical[88–94] 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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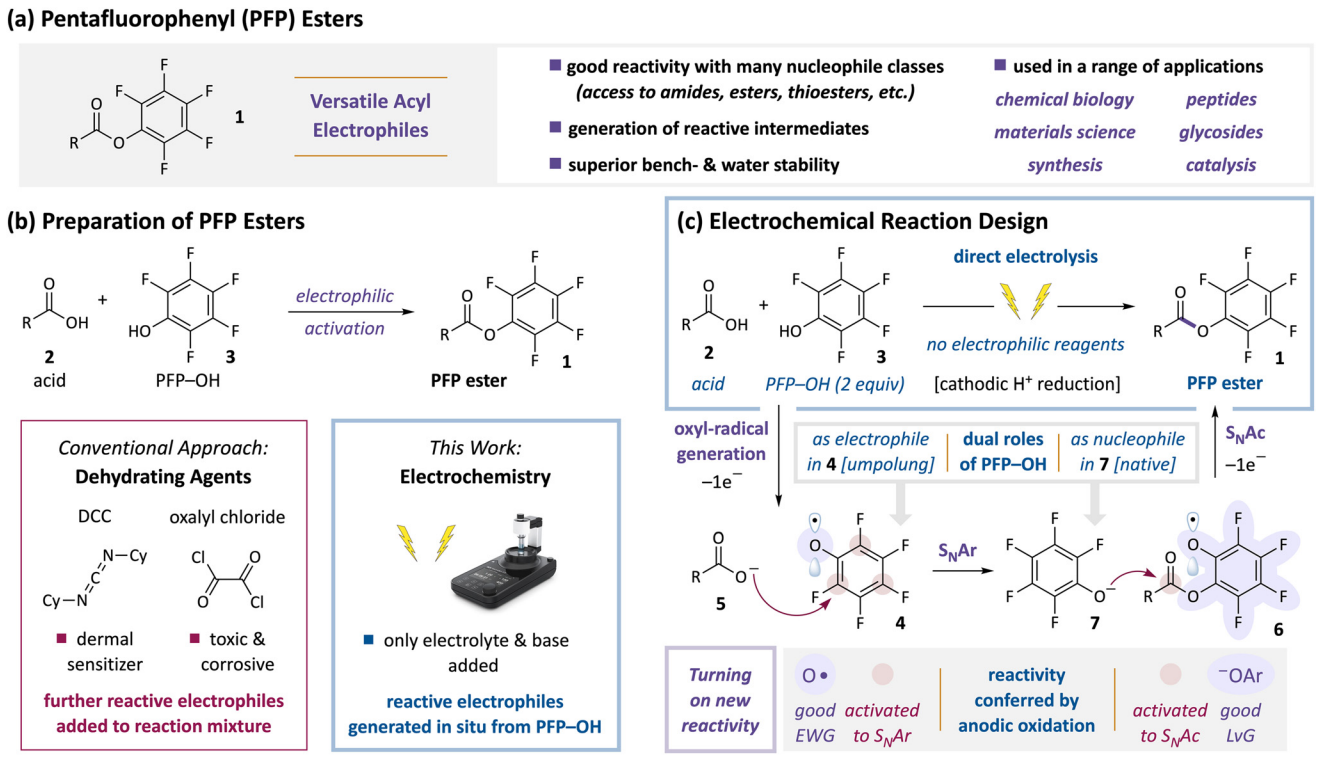


Fig. 1 (a) Pentafluorophenyl (PFP) esters are versatile acyl electrophiles that have been used in a range of applications. (b) PFP esters are conventionally prepared using electrophilic dehydrating agents. This work avoids the handling of reactive electrophiles since they are electrochemically generated them *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.

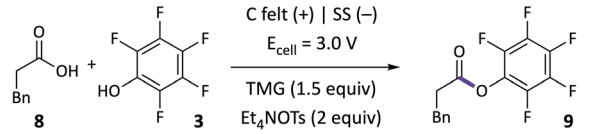
Design plan

Our reaction design (Fig. 1c) is initiated by deprotonation and single-electron anodic oxidation of PFP–OH (**3**, pK_a = 20.1 for PFP–OH[95] and E_p^{ox} = +0.27 V *vs.* SCE for $PFPO^-$, 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_NAr) by carboxylate ion **5**, owing to the exceptional electron-withdrawing character[96] 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_NAc, red shading on C) by PFP–O^- (**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_NAr that activates the carboxylic acid, and (2) as a native nucleophile for S_NAc, which forms the product.

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^1,N^1,N^2,N^2-tetramethylguanidine, TMG, 1.5 equiv.), and an electrolyte (Et_4NOTs, 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 (%)
electrodes entry 1	*graphite (+)* 58	*C felt (–)* 34	*Pt (–)* 87	– –	– –
electrolyte entry 2	*Bu_4NPF_6* 53	*Et_4NPF_6* 64	*Et_4NBF_4* 59	*Et_4NCl* 80	*Me_4NOH* 80 (no TMG)
eChem entry 3	*E_{cell} = 2.5 V* 30	*E_{cell} = 3.5 V* 77	*I = 15 mA* 88	*I = 25 mA* 32	– –
solvent entry 4	*DMF* 67	*DMSO* 10	*+5 eq H_2O* 75	*+10 eq H_2O* 66	– –
base entry 5	*Et_3N* 89	*DBU* 55	*Na_2CO_3* 15	*Na_3PO_4* 20	*NaOH* 9
[PFPOH] entry 6	*1 eq* 2	*2 eq* 15	*3 eq* 77	*4 eq* 83	*6 eq* 42
[PFPOH] 7 (1 eq TMG)	*1 eq* 3	*2 eq* 35	*3 eq* 87	*4 eq* 76	*5 eq* 69
atmosphere entry 8	*air* 0	*N_2 (no sparge)* 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_4NOTs (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 ^1H 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_6 and BF_4 electrolytes proved inferior to Et_4NOTs (53–64% yields, entries 2a–c), although Et_4NCl performed similarly (80% yield, entry 2d). Me_4NOH 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_3N 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_3 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 α-oxy acid and a variety of benzylic acids, which are potentially sensitive to oxidative decarboxylation,[97,98] 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,[16–20] materials chemistry,[23–31] and chemical biology,[37,38,41,42,45] 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 β-amino product **31** was obtained in 75% yield. The majority of our efforts then focused on α-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-

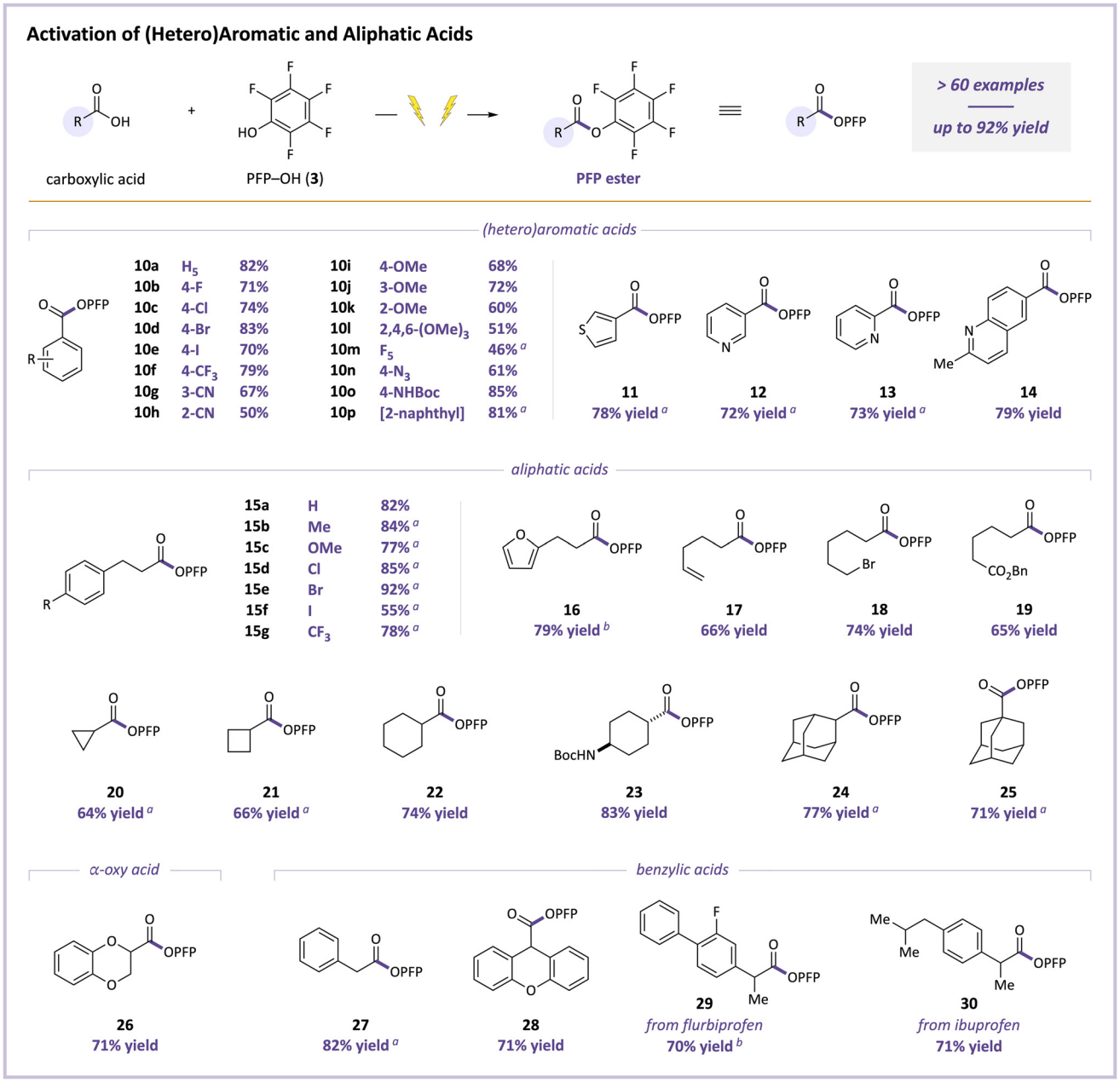


Fig. 3 Scope for PFP esterification of (hetero)aromatic and aliphatic acids. A mixture of acid (0.5 mmol, 1 equiv.), PFP–OH (**3**, 3–5 equiv.), TMG (1–1.5 equiv.), and Et_4NOTs (2 equiv.) in MeCN (0.05 M in acid) were electrolyzed at a constant cell potential of 3.0 V between a carbon-felt anode and stainless-steel cathode. Yields of isolated products. See ESI† for details. [a] Isolated as the corresponding *N*-benzylamide. [b] 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 α-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 ≥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,[39,40,43,44] 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

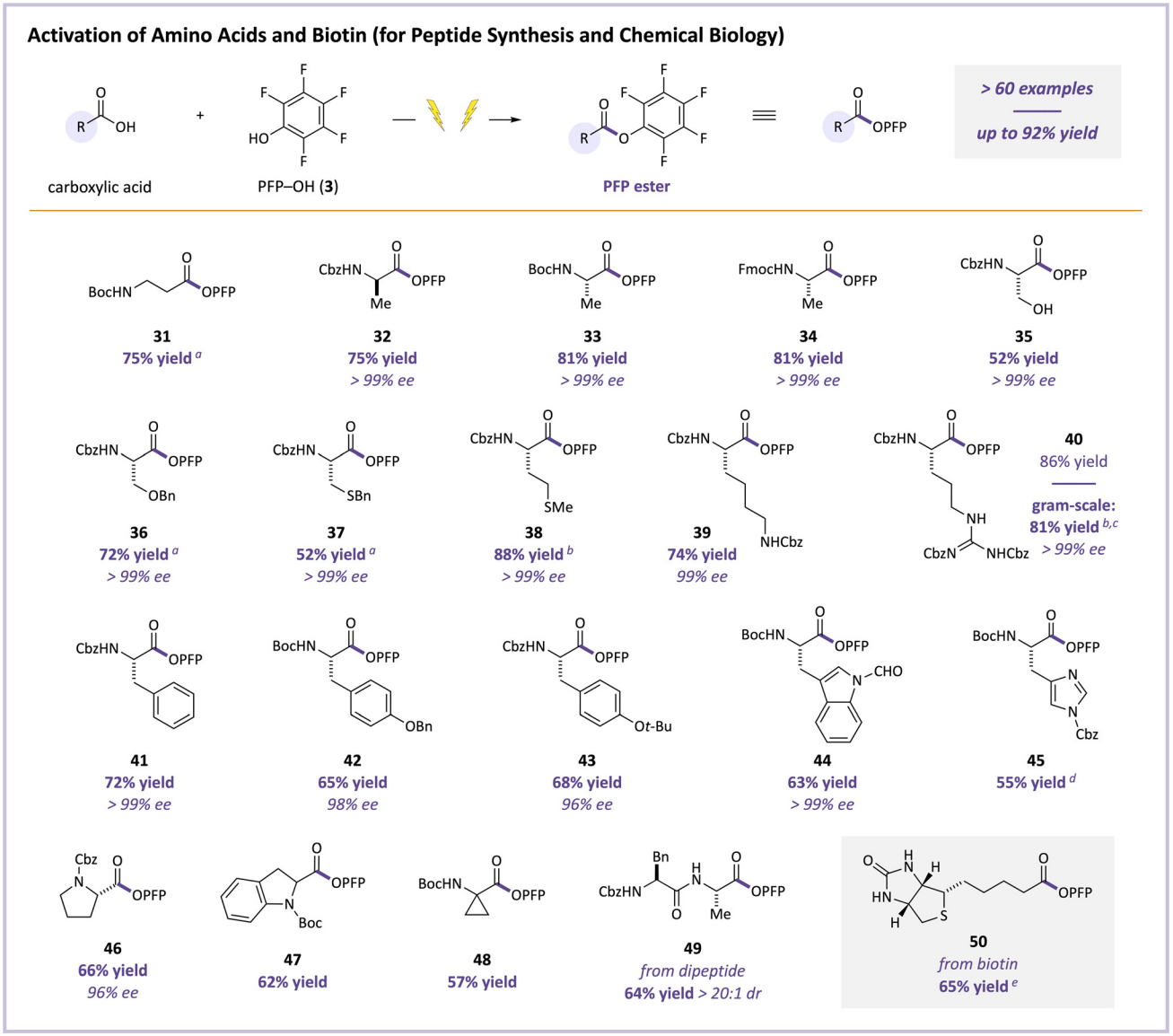


Fig. 4 Scope for PFP esterification of amino acids and biotin. A mixture of acid (0.5 mmol, 1 equiv.), PFP–OH (**3**, 3–5 equiv.), TMG (1–1.5 equiv.), and Et_4NOTs (2 equiv.) in MeCN (0.05 M in acid) were electrolyzed at a constant cell potential of 3.0 V between a carbon-felt anode and stainless-steel cathode. Yields of isolated products. See ESI† for details. [a] Isolated as the corresponding *N*-benylamide. [b] Performed on a larger scale (2 mmol of acid). [c] 3.5-V cell potential. [d] Yield determined by ^{19}F NMR. [e] 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_3N, 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.[99–101] Although these outcomes are consistent with the well-established performance of PFP esters in a range of applications,[16–55] 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.[102–109] 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

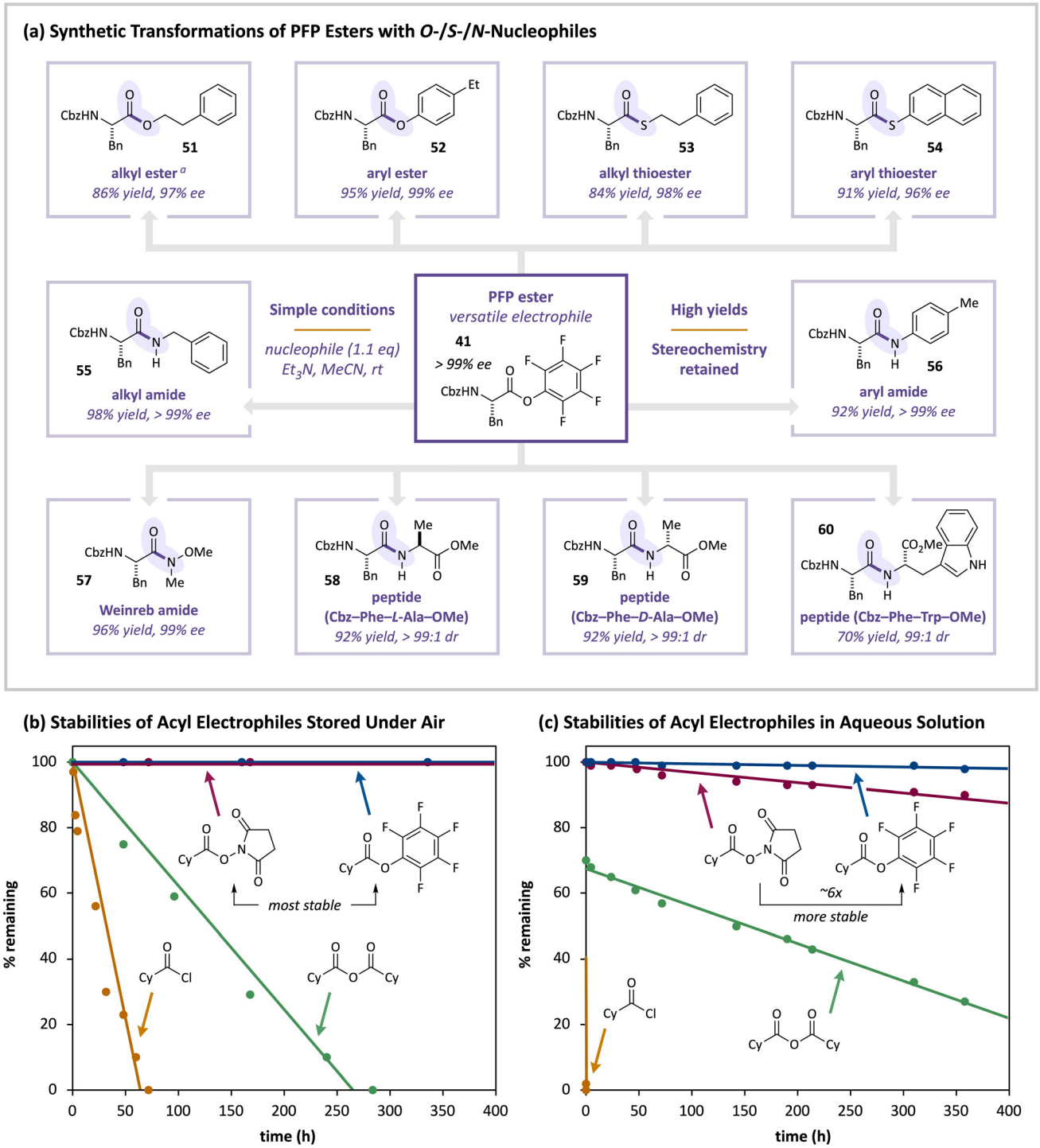


Fig. 5 (a) Synthetic transformations of amino-acid-derived PFP ester product **36**. A range of *O*-, *S*-, and *N*-nucleophiles efficiently generated the corresponding alkyl and aryl ester, thioester, and amide products, including a selection of dipeptides, with minimal racemization. Conditions: a solution of PFP ester **36** (0.5 mmol, 1 equiv.), nucleophile (1.1 equiv.), and Et_3N (1 equiv.) in MeCN (0.1 M in **36**) were stirred at rt. Yields of purified products are reported. See ESI† for details. [a] 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_3CN/D_2O), with % remaining measured by ^1H NMR analysis.

(Fig. 5c) by ^1H 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 electrochemical reaction. The standard base employed throughout these studies (TMG, pK_{BH+} = 23.4 in MeCN,[110] the standard reaction solvent) can deprotonate both the carboxylic acid (pK_a = 23.5 for AcOH in MeCN)[95] and PFP–OH (pK_a = 20.1 in MeCN),[95] 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$^-$ (**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 α-amino acids, benzylic acids, or dialkyl sulfides.

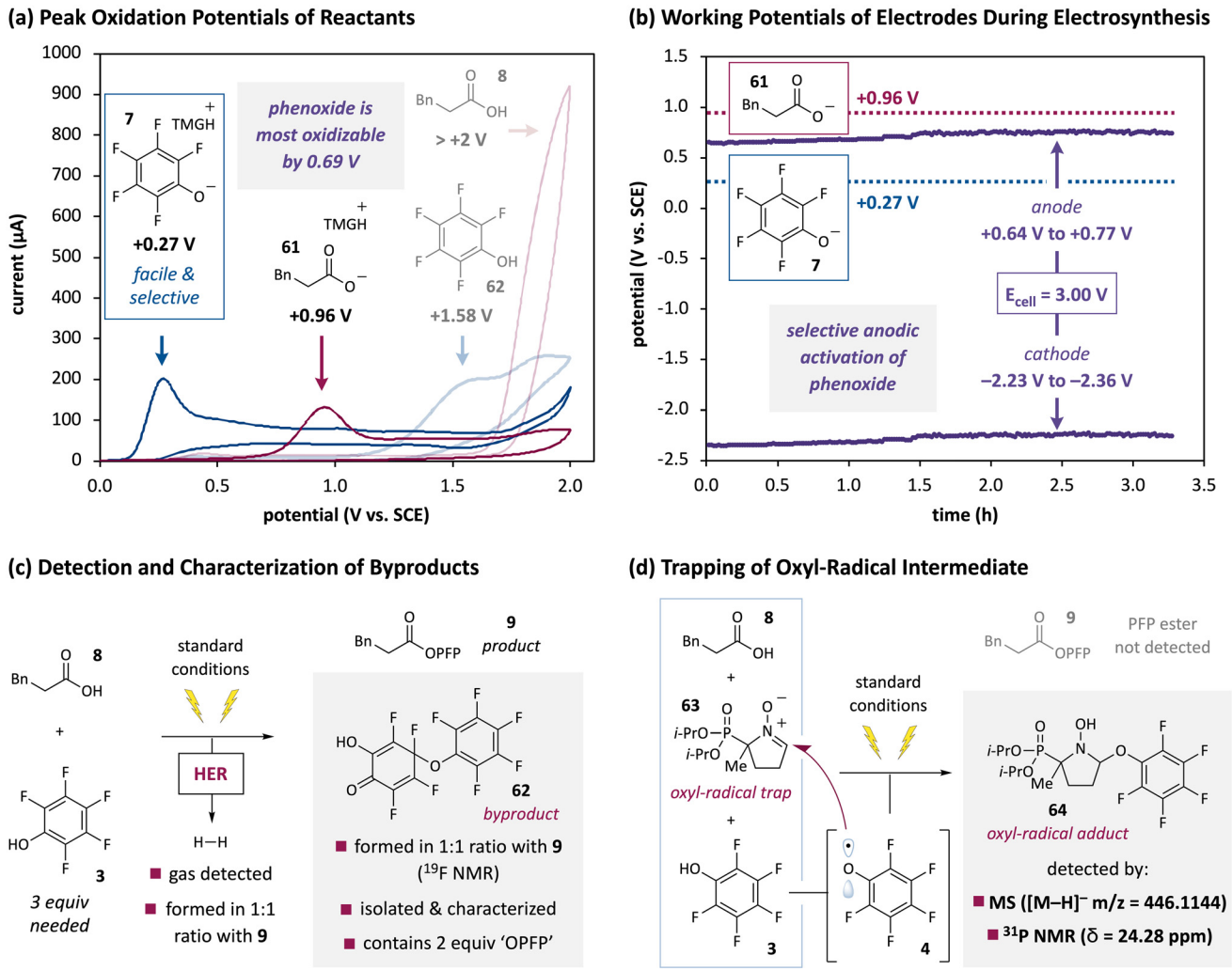


Fig. 6 Preliminary mechanistic experiments. (a) CV analyses revealed that the conjugate base of PFP–OH (phenoxide **7**) is oxidized at a significantly lower potential (+0.27 V *vs.* SCE) than any other possible major species in solution. (b) The potential of the anode varied from +0.64 V to +0.77 V *vs.* SCE during electrolysis, which can selectively engage phenoxide **7** while leaving carboxylates and other potentially oxidizable species intact. (c) Both H_2 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 ^{31}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$^-$ mixture present at any given time, but never reaches an energy that would destroy the carboxylate or other groups.[111]

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 ^{19}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_NAr,[96] was consistent with radical-trapping experiments (Fig. 6d). Addition of oxyl-radical trap **63**[112] to a standard preparative electrolysis completely prevented the formation of PFP ester **9**, and oxyl-radical adduct **64** was detected both by HRMS and ^{31}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_NAr by carboxylate ion **5**.[96] Putative intermediate **6** then undergoes a further anodic oxidation and is trapped by a second equivalent of PFP–O$^-$ (**7**), generating closed-shell acyl electrophile **65**. Finally, S_NAc with a third and final equivalent of PFP–O$^-$ (**7**) affords PFP ester **1** and byproduct **62**.

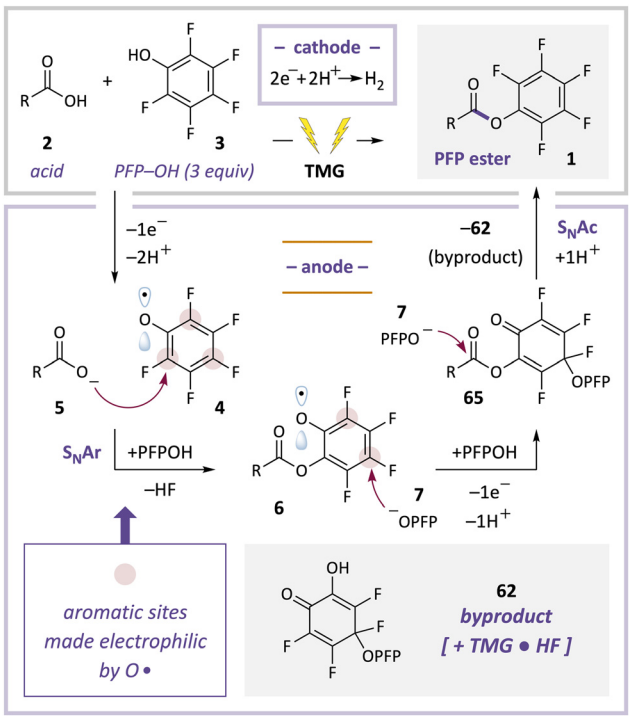


Fig. 7 Revised mechanistic hypothesis. Deprotonation and anodic oxidation of PFP–OH (**3**) generates oxyl radical **4**, which undergoes S_NAr with carboxylate **5**. Resulting open-shell *O*-aryl ester **6** is oxidized further and trapped by a second equivalent of PFP–O$^-$ (**7**), producing acyl electrophile **65**. S_NAc by a third equivalent of PFP–O$^-$ (**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_NAr/S_NAc 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).

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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References

1 K. M. Lokanatha Rai, *Carbonyl Compounds - Chemistry and Synthetic Applications*, Notion Press Media, 2020.
2 *Comprehensive Organic Synthesis*, ed. P. Knochel, Elsevier, Amsterdam, 2nd edn, 2014, vol 6, pp. 296-597.
3 K. P. C. Vollhardt and N. E. Schore, in *Organic Chemistry: Structure and Function*, W. H. Freeman and Company, New York, NY, 5th edn, 2007, ch. 19, pp. 856–908.
4 J. D. Roberts and M. C. Caserio, *Basic Principles of Organic Chemistry*, W. A. Benjamin, Inc., New York, NY, USA, 1965.
5 J. Yang, H. Huang and J. Zhao, Active ester-based peptide bond formation and its application in peptide synthesis, *Org. Chem. Front.*, 2023, **10**, 1817–1846.
6 J. Dussart-Gautheret, J. Deschamp, M. Monteil, O. Gager, T. Legigan, E. Migianu-Griffoni and M. Lecouvey, Formation of 1-Hydroxymethylene-1,1-bisphosphinates through the Addition of a Silylated Phosphonite on Various Trivalent Derivatives, *J. Org. Chem.*, 2020, **85**, 14559–14569.
7 M. Bodanszky and A. Bodanszky, in *The Practice of Peptide Synthesis*, Springer, Berlin, 2nd edn, 1994, pp. 96–107.
8 L. Kisfaludy, T. Mohacsi, M. Low and F. Drexler, Pentafluorophenyl acetate: a new, highly selective acetylating agent, *J. Org. Chem.*, 1979, **44**, 654–656.
9 R. B. Merrifield, Solid Phase Peptide Synthesis. I. The Synthesis of a Tetrapeptide, *J. Am. Chem. Soc.*, 1963, **85**, 2149–2154.
10 D. Stefanidis, S. Cho, S. Dhe-Paganon and W. P. Jencks, Structure-reactivity correlations for reactions of substituted phenolate anions with acetate and formate esters, *J. Am. Chem. Soc.*, 1993, **115**, 1650–1656.
11 D. G. McCarthy, A. F. Hegarty and B. J. Hathaway, N-hydroxy-compounds as acyl transfer agents. Part 1. Kinetics and mechanism of nucleophilic displacements on 1-hydroxybenzotriazole esters and crystal and molecular structure of 1-benzoyloxybenzotriazole, *J. Chem. Soc., Perkin Trans. 2*, 1977, 224–231.
12 D. E. Ames and T. F. Grey, The synthesis of some N-hydroxyimides, *J. Chem. Soc.*, 1955, 631–636.
13 C. Ma, M. Chen, W. Chu, J. Tao, D. Kong, M. Zhang and W. Feng, A Practical and Total Synthesis of Pasireotide: Synthesis of Cyclic Hexapeptide via a Three-Component Condensation, *Molecules*, 2019, **24**, 2185.
14 S. Asano, J. T. Patterson, T. Gaj and C. F. Barbas, 3rd, Site-selective labeling of a lysine residue in human serum albumin, *Angew. Chem., Int. Ed.*, 2014, **53**, 11783–11786.
15 G. W. Anderson, J. E. Zimmerman and F. M. Callahan, N-Hydroxysuccinimide Esters in Peptide Synthesis, *J. Am. Chem. Soc.*, 1963, **85**, 3039–3039.
16 A. Wu and H. Yamamoto, Super silyl-based stable protecting groups for both the C- and N-terminals of peptides: applied as effective hydrophobic tags in liquid-phase peptide synthesis, *Chem. Sci.*, 2023, **14**, 5051–5061.
17 A. T. Ślósarczyk, R. Ramapanicker, T. Norberg and L. Baltzer, Mixed pentafluorophenyl and o-fluorophenyl esters of aliphatic dicarboxylic acids: efficient tools for peptide and protein conjugation, *RSC Adv.*, 2012, **2**, 908–914.
18 C. A. G. N. Montalbetti and V. Falque, Amide bond formation and peptide coupling, *Tetrahedron*, 2005, **61**, 10827–10852.
19 V. N. Karel'skii, E. P. Krysin, A. A. Antonov and G. E. Rostovskaya, Use of pentafluorophenyl esters in the synthesis of intermediate fragments of ACTH, *Chem. Nat. Compd.*, 1982, **18**, 90–94.
20 L. Kisfaludy, J. E. Roberts, R. H. Johnson, G. L. Mayers and J. Kovacs, Synthesis of N-carbobenzoxyamino acid and peptide pentafluorophenyl esters as intermediates in peptide synthesis, *J. Org. Chem.*, 1970, **35**, 3563–3565.
21 A. Imamura, A. Kimura, H. Ando, H. Ishida and M. Kiso, Extended applications of di-tert-butylsilylene-directed alpha-predominant galactosylation compatible with C2-participating groups toward the assembly of various glycosides, *Chem. – Eur. J.*, 2006, **12**, 8862–8870.
22 H. Ando, A. Imamura, M. Kiso and H. Ishida, Method of Alpha-Selective Glycosylation, *European Patent*, 1,626,053 A2, 2004.
23 J. J. Tarrio, R. Rodriguez, B. Fernandez, E. Quinoa and F. Freire, Dissymmetric Chiral Poly(diphenylacetylene)s: Secondary Structure Elucidation and Dynamic Luminescence, *Angew. Chem., Int. Ed.*, 2022, **61**, e202115070.
24 A. P. P. Kröger, J.-W. D. Paats, R. J. E. A. Boonen, N. M. Hamelmann and J. M. J. Paulusse, Pentafluorophenyl-based single-chain polymer nanoparticles as a versatile platform towards protein mimicry, *Polym. Chem.*, 2020, **11**, 6056–6065.
25 D. P. Sanders, K. Fukushima, D. J. Coady, A. Nelson, M. Fujiwara, M. Yasumoto and J. L. Hedrick, A simple and efficient synthesis of functionalized cyclic carbonate monomers using a versatile pentafluorophenyl ester intermediate, *J. Am. Chem. Soc.*, 2010, **132**, 14724–14726.

26 P. J. Roth, K. T. Wiss, R. Zentel and P. Theato, Synthesis of Reactive Telechelic Polymers Based on Pentafluorophenyl Esters, *Macromolecules*, 2008, **41**, 8513–8519.
27 M. M. Dominguez, M. Wathier, M. W. Grinstaff and S. E. Schaus, Immobilized hydrogels for screening of molecular interactions, *Anal. Chem.*, 2007, **79**, 1064–1066.
28 M. W. Grinstafe, J. Butlin, M. A. Carnahan, K. R. D'Alessio and T. P. Hickey, Low-Swelling Hydrogel Sealants for Wound Repair, *World Patent*, 2007/001926 A2, 2007.
29 M. W. Grinstafe and M. A. Carnahan, Dendritic Polymers, Crosslinked Gels, and Their Uses as Ophthalmic Sealants and Lenses, *World Patent*, 2006/031358 A2, 2006.
30 M. Eberhardt, R. Mruk, R. Zentel and P. Théato, Synthesis of pentafluorophenyl(meth)acrylate polymers: New precursor polymers for the synthesis of multifunctional materials, *Eur. Polym. J.*, 2005, **41**, 1569–1575.
31 M. Wathier, P. J. Jung, M. A. Carnahan, T. Kim and M. W. Grinstaff, Dendritic macromers as in situ polymerizing biomaterials for securing cataract incisions, *J. Am. Chem. Soc.*, 2004, **126**, 12744–12745.
32 M. Calvert, R. P. Sweeney, H. M. Chen, H. Bajwa, S. A. Nasseri, D. Habibi and S. G. Withers, Branched montbretin A mimics allow derivatisation and potent amylase inhibition, *Org. Biomol. Chem.*, 2023, **21**, 7977–7983.
33 G. Bernardes, L. Couturier, J. Becher and E. Gil de Montes Rojas, Quinone Protected Forms and Conjugates, *World Patent*, 2023/227757 A1, 2023.
34 S. Nasim, S. Pei, F. K. Hagen, C. T. Jordan and P. A. Crooks, Melampomagnolide B: a new antileukemic sesquiterpene, *Bioorg. Med. Chem.*, 2011, **19**, 1515–1519.
35 A. Homma, H. Sato, T. Tamura, A. Okamachi, T. Emura, T. Ishizawa, T. Kato, T. Matsuura, S. Sato, Y. Higuchi, T. Watanabe, H. Kitamura, K. Asanuma, T. Yamazaki, M. Ikemi, H. Kitagawa, T. Morikawa, H. Ikeya, K. Maeda, K. Takahashi, K. Nohmi, N. Izutani, M. Kanda and R. Suzuki, Synthesis and optimization of hyaluronic acid-methotrexate conjugates to maximize benefit in the treatment of osteoarthritis, *Bioorg. Med. Chem.*, 2010, **18**, 1062–1075.
36 S. Lociuro, P. Tavecchia, R. Ciabatti and E. Restelli, Derivatives of Antibiotic GE2270 Factors C2A, D2, and E, *US Patent*, 6,008,225 A, 1999.
37 H. Ren, Q. Hu, J. Yang, X. Zhou, X. Liu, J. Tang, H. Hu, Y. Shen and Z. Zhou, Single-Molecule Dendritic MRI Nanoprobes Reveal the Size-Dependent Tumor Entrance, *Adv. Healthcare Mater.*, 2023, **12**, e2302210.
38 H. Ren, Q. Hu, Y. Sun, X. Zhou, Y. Zhu, Q. Dong, L. Chen, J. Tang, H. Hu, Y. Shen and Z. Zhou, Surface chemistry mediates the tumor entrance of nanoparticles probed using single-molecule dual-imaging nanodots, *Biomater. Sci.*, 2023, **11**, 7051–7061.
39 V. Waser, M. Mukherjee, R. Tachibana, N. V. Igareta and T. R. Ward, An Artificial $[Fe_4S_4]$-Containing Metalloenzyme for the Reduction of CO_2 to Hydrocarbons, *J. Am. Chem. Soc.*, 2023, **145**, 14823–14830.
40 W. Wang, R. Tachibana, Z. Zou, D. Chen, X. Zhang, K. Lau, F. Pojer, T. R. Ward and X. Hu, Manganese Transfer Hydrogenases Based on the Biotin-Streptavidin Technology, *Angew. Chem., Int. Ed.*, 2023, **62**, e202311896.
41 D. Kang, S. Lee and J. Kim, Bioorthogonal Click and Release: A General, Rapid, Chemically Revertible Bioconjugation Strategy Employing Enamine N-oxides, *Chem*, 2022, **8**, 2260–2277.
42 M. Scherer, K. Fischer, F. Depoix, T. Fritz, R. Thiermann, K. Mohr and R. Zentel, Pentafluorophenyl Ester-based Polymersomes as Nanosized Drug-Delivery Vehicles, *Macromol. Rapid Commun.*, 2016, **37**, 60–66.
43 J. M. Chambers, L. M. Lindqvist, A. Webb, D. C. Huang, G. P. Savage and M. A. Rizzacasa, Synthesis of biotinylated episilvestrol: highly selective targeting of the translation factors eIF4AI/II, *Org. Lett.*, 2013, **15**, 1406–1409.
44 L. Dafik, V. Kalsani, A. K. Leung and K. Kumar, Fluorinated lipid constructs permit facile passage of molecular cargo into living cells, *J. Am. Chem. Soc.*, 2009, **131**, 12091–12093.
45 R. Kluger and A. Alagic, Chemical cross-linking and protein-protein interactions-a review with illustrative protocols, *Bioorg. Chem.*, 2004, **32**, 451–472.
46 H. K. Banovetz, K. L. Vickerman, C. M. David, M. Alkan and L. M. Stanley, Palladium-Catalyzed Intermolecular Alkene Carboacylation via Ester C-O Bond Activation, *Org. Lett.*, 2021, **23**, 3507–3512.
47 H. Li, Y. Hou, C. Liu, Z. Lai, L. Ning, R. Szostak, M. Szostak and J. An, Pentafluorophenyl Esters: Highly Chemoselective Ketyl Precursors for the Synthesis of α,α-Dideuterio Alcohols Using SmI_2 and D_2O as a Deuterium Source, *Org. Lett.*, 2020, **22**, 1249–1253.
48 J. Buchspies, D. J. Pyle, H. He and M. Szostak, Pd-Catalyzed Suzuki-Miyaura Cross-Coupling of Pentafluorophenyl Esters, *Molecules*, 2018, **23**, 3134.
49 S. Specklin and J. Cossy, Chemoselective synthesis of beta-ketophosphonates using lithiated alpha-(trimethylsilyl) methylphosphonate, *J. Org. Chem.*, 2015, **80**, 3302–3308.
50 B. G. Avitabile, C. A. Smith and D. B. Judd, Pentafluorophenyl sulfonate ester as a protecting group for the preparation of biaryl- and heterobiaryl sulfonate esters, *Org. Lett.*, 2005, **7**, 843–846.
51 M. Zhu, P. Wang, Q. Zhang, W. Tang and W. Zi, Diastereodivergent Aldol-Type Coupling of Alkoxyallenes with Pentafluorophenyl Esters Enabled by Synergistic Palladium/Chiral Lewis Base Catalysis, *Angew. Chem., Int. Ed.*, 2022, **61**, e202207621.
52 Q. Zhang, M. Zhu and W. Zi, Synergizing palladium with Lewis base catalysis for stereodivergent coupling of 1,3-dienes with pentafluorophenyl acetates, *Chem*, 2022, **8**, 2784–2796.
53 K. J. Schwarz, C. M. Pearson, G. A. Cintron-Rosado, P. Liu and T. N. Snaddon, Traversing Steric Limitations by Cooperative Lewis Base/Palladium Catalysis: An Enantioselective Synthesis of alpha-Branched Esters Using 2-Substituted Allyl Electrophiles, *Angew. Chem., Int. Ed.*, 2018, **57**, 7800–7803.
54 L. Hutchings-Goetz, C. Yang and T. N. Snaddon, Enantioselective alpha-Allylation of Aryl Acetic Acid Esters

via C1-Ammonium Enolate Nucleophiles: Identification of a Broadly Effective Palladium Catalyst for Electron-Deficient Electrophiles, *ACS Catal.*, 2018, **8**, 10537–10544.

55 K. J. Schwarz, J. L. Amos, J. C. Klein, D. T. Do and T. N. Snaddon, Uniting C1-Ammonium Enolates and Transition Metal Electrophiles via Cooperative Catalysis: The Direct Asymmetric alpha-Allylation of Aryl Acetic Acid Esters, *J. Am. Chem. Soc.*, 2016, **138**, 5214–5217.

56 H. Ando and A. Imamura, Method of Alpha-Selective Glycosylation, *European Patent*, 1,626,053 A2, 2004.

57 M. Adamczyk, J. R. Fishpaugh and K. J. Heuser, Preparation of succinimidyl and pentafluorophenyl active esters of 5- and 6-carboxyfluorescein, *Bioconjugate Chem.*, 1997, **8**, 253–255.

58 Despite significant progress in the activation of acids (see following reference), the poor nucleophilicity of PFP–OH in its neutral form may account for its complete absence as a reported nucleophile in any of these methods.

59 J. Zhou, M. Paladino and D. G. Hall, Direct Boronic Acid Promoted Amidation of Carboxylic Acids with Poorly Nucleophilic Amines, *Eur. J. Org. Chem.*, 2022, e202201050.

60 Y. Zheng, Y. Zhao, S. Tao, X. Li, X. Cheng, G. Jiang and X. Wan, Green Esterification of Carboxylic Acids Promoted by tert–Butyl Nitrite, *Eur. J. Org. Chem.*, 2021, 2713–2718.

61 S. Nagahara, Y. Okada, Y. Kitano and K. Chiba, Biphasic electrochemical peptide synthesis, *Chem. Sci.*, 2021, **12**, 12911–12917.

62 L. A. Wolzak, J. I. Vlugt, K. J. Berg, J. N. H. Reek, M. Tromp and T. J. Korstanje, Titanium–catalyzed esterification reactions: beyond Lewis acidity, *ChemCatChem*, 2020, **12**, 5229–5235.

63 Handoko, S. Satishkumar, N. R. Panigrahi and P. S. Arora, Rational Design of an Organocatalyst for Peptide Bond Formation, *J. Am. Chem. Soc.*, 2019, **141**, 15977–15985.

64 Z. Liu, H. Noda, M. Shibasaki and N. Kumagai, Catalytic Oligopeptide Synthesis, *Org. Lett.*, 2018, **20**, 612–615.

65 H. Noda, M. Furutachi, Y. Asada, M. Shibasaki and N. Kumagai, Unique physicochemical and catalytic properties dictated by the B_3NO_2 ring system, *Nat. Chem.*, 2017, **9**, 571–577.

66 H. Lundberg, F. Tinnis and H. Adolfsson, Direct amide coupling of non-activated carboxylic acids and amines catalysed by zirconium(IV) chloride, *Chem. – Eur. J.*, 2012, **18**, 3822–3826.

67 N. Gernigon, R. M. Al-Zoubi and D. G. Hall, Direct amidation of carboxylic acids catalyzed by ortho-iodo arylboronic acids: catalyst optimization, scope, and preliminary mechanistic study supporting a peculiar halogen acceleration effect, *J. Org. Chem.*, 2012, 77, 8386–8400.

68 H. Adolfsson, H. Lundberg and F. Tinnis, Titanium(IV) Isopropoxide as an Efficient Catalyst for Direct Amidation of Nonactivated Carboxylic Acids, *Synlett*, 2012, 2201–2204.

69 R. M. Al-Zoubi, O. Marion and D. G. Hall, Direct and waste-free amidations and cycloadditions by organocatalytic activation of carboxylic acids at room temperature, *Angew. Chem., Int. Ed.*, 2008, **47**, 2876–2879.

70 R. K. Mylavarapu, K. Gcm, N. Kolla, R. Veeramalla, P. Koilkonda, A. Bhattacharya and R. Bandichhor, Boric Acid Catalyzed Amidation in the Synthesis of Active Pharmaceutical Ingredients, *Org. Process Res. Dev.*, 2007, **11**, 1065–1068.

71 T. Funatomi, K. Wakasugi, T. Misaki and Y. Tanabe, Pentafluorophenylammonium triflate (PFPAT): an efficient, practical, and cost-effective catalyst for esterification, thioesterification, transesterification, and macrolactone formation, *Green Chem.*, 2006, **8**, 1022–1027.

72 K. Ishihara, M. Nakayama, S. Ohara and H. Yamamoto, Direct ester condensation from a 1 : 1 mixture of carboxylic acids and alcohols catalyzed by hafnium(IV) or zirconium(IV) salts, *Tetrahedron*, 2002, **58**, 8179–8188.

73 K. Manabe, X. M. Sun and S. Kobayashi, Dehydration reactions in water. Surfactant-type Bronsted acid-catalyzed direct esterification of carboxylic acids with alcohols in an emulsion system, *J. Am. Chem. Soc.*, 2001, **123**, 10101–10102.

74 K. Wakasugi, T. Misaki, K. Yamada and Y. Tanabe, Diphenylammonium triflate (DPAT): efficient catalyst for esterification of carboxylic acids and for transesterification of carboxylic esters with nearly equimolar amounts of alcohols, *Tetrahedron Lett.*, 2000, **41**, 5249–5252.

75 K. Ishihara, S. Ohara and H. Yamamoto, Direct condensation of carboxylic acids with alcohols catalyzed by Hafnium(IV) salts, *Science*, 2000, **290**, 1140–1142.

76 K. Ishihara and H. Yamamoto, Arylboron Compounds as Acid Catalysts in Organic Synthetic Transformations, *Eur. J. Org. Chem.*, 1999, 527–538.

77 Y. Masaki, N. Tanaka and T. Miura, Mild Esterification and Transesterification of Carboxylic Acids Catalyzed by Tetracyanoethylene and Dicyanoketene Dimethyl Acetal, *Chem. Lett.*, 1997, **26**, 55–56.

78 K. Ishihara, S. Ohara and H. Yamamoto, 3,4,5-Trifluorobenzeneboronic Acid as an Extremely Active Amidation Catalyst, *J. Org. Chem.*, 1996, **61**, 4196–4197.

79 J. Otera, N. Danoh and H. Nozaki, Novel template effects of distannoxane catalysts in highly efficient transesterification and esterification, *J. Org. Chem.*, 1991, **56**, 5307–5311.

80 S. J. Barbee, J. J. Stone and R. J. Hilaski, Acute inhalation toxicology of oxalyl chloride, *Am. Ind. Hyg. Assoc. J.*, 1995, **56**, 74–76.

81 J. Pauluhn, *Study for Acute Inhalation Toxicity in Rats in Accordance with OECD Guideline No. 403 (Exposure: 1 × 1 Hour)*, Bayer AG, Leverkusen, Germany, 1987.

82 M. Matsumoto, H. Ito, A. Tateishi, Y. Kobayashi, K. Satoh, K. Numata and H. Miyakawa, Effects of polycaprolactone degradation products on the water flea, Daphnia magna: Carbodiimide additives have acute and chronic toxicity, *J. Appl. Toxicol.*, 2023, **43**, 1840–1848.

83 I. Surh, M. Behl, S. A. Elmore and R. S. Chhabra, Comparative dermal toxicity of dicyclohexylcarbodiimide

and diisopropylcarbodiimide in rodents, *Cutaneous Ocul. Toxicol.*, 2012, **31**, 177–187.

84 National Toxicology Program, NTP Report on the Toxicology Study of Diispropylcarbodiimide (CAS No. 693-13-0) in Genetically Modified (FVB Tg.AC Hemizygous) Mice and Carcinogenicity Study of Diispropylcarbodiimide in Genetically Modified [B6.129-Trp53tm1Brd (N5) Haploinsufficient] Mice (Dermal Studies), Report NTP GMM 10, 2007.

85 National Toxicology Program, NTP Genetically Modified Model Report on the Toxicology Studies of Dicyclohexylcarbodiimide (CASRN 538-75-0) in F344/N Rats, B6C3F1 Mice, and Genetically Modified (FVB Tg.AC Hemizygous) Mice and Carcinogenicity Study of Dicyclohexylcarbodiimide in Genetically Modified [B6.129-Trp53tm1Brd (N5) Haploinsufficient] Mice (Dermal Studies), Report NTP GMM 09, 2007.

86 National Toxicology Program, Toxicology and Carcinogenesis Studies of Diisopropylcarbodiimide in F344/N Rats and B6C3F1 Mice (Dermal Studies), Report NTP TR 523, 2007.

87 A. B. Moshnikova, V. N. Afanasyev, O. V. Proussakova, S. Chernyshov, V. Gogvadze and I. P. Beletsky, Cytotoxic activity of 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide is underlain by DNA interchain cross-linking, *Cell. Mol. Life Sci.*, 2006, **63**, 229–234.

88 M. C. Leech and K. Lam, A practical guide to electrosynthesis, *Nat. Rev. Chem.*, 2022, **6**, 275–286.

89 E. O. Bortnikov and S. N. Semenov, Unconventional approaches for organic electrosynthesis: Recent progress, *Curr. Opin. Electrochem.*, 2022, **35**, 101050.

90 J. C. Siu, N. Fu and S. Lin, Catalyzing Electrosynthesis: A Homogeneous Electrocatalytic Approach to Reaction Discovery, *Acc. Chem. Res.*, 2020, **53**, 547–560.

91 C. Schotten, T. P. Nicholls, R. A. Bourne, N. Kapur, B. N. Nguyen and C. E. Willans, Making electrochemistry easily accessible to the synthetic chemist, *Green Chem.*, 2020, **22**, 3358–3375.

92 M. C. Leech, A. D. Garcia, A. Petti, A. P. Dobbs and K. Lam, Organic electrosynthesis: from academia to industry, *React. Chem. Eng.*, 2020, **5**, 977–990.

93 A. Wiebe, T. Gieshoff, S. Mohle, E. Rodrigo, M. Zirbes and S. R. Waldvogel, Electrifying Organic Synthesis, *Angew. Chem., Int. Ed.*, 2018, **57**, 5594–5619.

94 M. Yan, Y. Kawamata and P. S. Baran, Synthetic Organic Electrochemical Methods Since 2000: On the Verge of a Renaissance, *Chem. Rev.*, 2017, **117**, 13230–13319.

95 A. Kütt, S. Tshepelevitsh, J. Saame, M. Lõkov, I. Kaljurand, S. Selberg and I. Leito, Strengths of Acids in Acetonitrile, *Eur. J. Org. Chem.*, 2021, 1407–1419.

96 N. Y. Shin, E. Tsui, A. Reinhold, G. D. Scholes, M. J. Bird and R. R. Knowles, Radicals as Exceptional Electron-Withdrawing Groups: Nucleophilic Aromatic Substitution of Halophenols Via Homolysis-Enabled Electronic Activation, *J. Am. Chem. Soc.*, 2022, **144**, 21783–21790.

97 M. K. Abdel Latif, J. N. Spencer, B. E. Kidd, L. A. Madsen and J. M. Tanko, Electrochemical Oxidation of Aliphatic Carboxylates: Kinetics, Thermodynamics, Mechanism, and the Role of Hydrogen Bonding, *ChemElectroChem*, 2024, **11**, e202300514.

98 J. Hioe and H. Zipse, Radical stability and its role in synthesis and catalysis, *Org. Biomol. Chem.*, 2010, **8**, 3609–3617.

99 Y. Zhou, H. Li, Y. Huang, J. Li, G. Deng, G. Chen, Z. Xi and C. Zhou, Suppression of alpha-carbon racemization in peptide synthesis based on a thiol-labile amino protecting group, *Nat. Commun.*, 2023, **14**, 5324.

100 L. Ferrazzano, M. Catani, A. Cavazzini, G. Martelli, D. Corbisiero, P. Cantelmi, T. Fantoni, A. Mattellone, C. De Luca, S. Felletti, W. Cabri and A. Tolomelli, Sustainability in peptide chemistry: current synthesis and purification technologies and future challenges, *Green Chem.*, 2022, **24**, 975–1020.

101 S. Carganico and A. M. Papini, in *Amino Acids, Peptides and Proteins in Organic Chemistry: Building Blocks, Catalysis and Coupling Chemistry*, ed. A. B. Hughes, Wiley–VCH Verlag GmbH & Co. KGaA, 2011, vol. 3, ch. 9, pp. 313–348.

102 N. Sugisawa, A. Ando and S. Fuse, Rapid and column-chromatography-free peptide chain elongation via a one-flow, three-component coupling approach, *Chem. Sci.*, 2023, **14**, 6986–6991.

103 D. Jang and J.-G. Kim, A Convenient, One-Pot Procedure for the Preparation of Acyl and Sulfonyl Fluorides Using Cl_3CCN, Ph_3P, and $TBAF(t\text{-}BuOH)_4$, *Synlett*, 2010, 3049–3052.

104 M. P. Paradisi, G. P. Zecchini, I. Torrini and G. Lucente, Synthesis, stereochemistry and conformational properties of diastereomeric cyclic dipeptides containing tetrahydro–1,4–thiazine–3,5–dicarboxylic acid, *J. Heterocycl. Chem.*, 2009, **27**, 1661–1664.

105 G. Evindar and R. A. Batey, Parallel synthesis of a library of benzoxazoles and benzothiazoles using ligand-accelerated copper-catalyzed cyclizations of ortho-halobenzanilides, *J. Org. Chem.*, 2006, **71**, 1802–1808.

106 U. Schmidt, U. Beutler and A. Lieberknecht, Total Synthesis of the Antitumor Antibiotic WF–3161, *Angew. Chem., Int. Ed.*, 2003, **28**, 333–334.

107 K. Hirai, H. Koike, T. Ishiba, S. Ueda, I. Makino, H. Yamada, T. Ichihashi, Y. Mizushima, M. Ishikawa, Y. Ishihara, Y. Hara, H. Hirose, N. Shima and M. Doteuchi, Amino acid amides of 2-[(2-aminobenzyl) sulfinyl]benzimidazole as acid-stable prodrugs of potential inhibitors of H + K+ ATPase, *Eur. J. Med. Chem.*, 1991, **26**, 143–158.

108 U. Schmidt, M. Kroner and U. Beutler, Amino Acids and Peptides; 67.1 Easy Preparation and Use of Benzyloxycarbonyl Derivatives of Amino Acid Chlorides and α-Hydroxycarboxylic Acid Chlorides, *Synthesis*, 1988, 475–477.

109 O. Dangles, F. Guibe, G. Balavoine, S. Lavielle and A. Marquet, Selective cleavage of the allyl and (allyloxy)carbonyl groups through palladium-catalyzed hydrostannolysis with tributyltin hydride. Application to the selective protection-deprotection of amino acid derivatives and in peptide synthesis, *J. Org. Chem.*, 1987, **52**, 4984–4993.

110 S. Tshepelevitsh, A. Kütt, M. Lõkov, I. Kaljurand, J. Saame, A. Heering, P. G. Plieger, R. Vianello and I. Leito, On the Basicity of Organic Bases in Different Media, *Eur. J. Org. Chem.*, 2019, 6735–6748.

111 D. Nicewicz, H. Roth and N. Romero, Experimental and Calculated Electrochemical Potentials of Common Organic Molecules for Applications to Single-Electron Redox Chemistry, *Synlett*, 2015, 714–723.

112 L. Zoia and D. S. Argyropoulos, Phenoxy radical detection using ^{31}P NMR spin trapping, *J. Phys. Org. Chem.*, 2009, **22**, 1070–1077.