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Electrochemical synthesis of aziridines, pyrrolidines and oxazolines enabled by azo-free alcohol amination†

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Although amines and nitrogen-containing heterocycles are prominent scaffolds in bioactive compounds, functional materials, and commodity chemicals, their synthesis and functionalization often suffer from lengthy pre-installation of the appropriate functional groups, employing exotic amination/aziridination reagents and the use of expensive or toxic catalysts. Herein, we developed a mild and economical electrochemical amination method to access aziridine, pyrrolidine and oxazoline motifs from the corresponding amino alcohol substrates. Compared to the classic Mitsunobu reaction, this method exhibits an expanded scope of nucleophiles, including weakly acidic amides and primary amines. Mechanistic studies provided direct evidence for the proposed two-electron oxidation of alcohol and PPh_3 to yield the alkoxyphosphonium cation intermediate. This reaction demonstrates the potential of using electrochemistry to not only replace azo-oxidants in classic Mitsunobu reactions, but also improve the synthetic applicability by overcoming the $\text{p}K_{\text{a}}$ limit due to the azo-derived betaine intermediate.

Nitrogen heterocycles, such as aziridines, are prevalent synthetic targets in multiple research fields, including medicinal chemistry, the agricultural industry and materials science, due to their versatile reactivities and engaged interaction modes with metal cations and Brønsted acids, such as coordination and hydrogen-bonding aggregation.^{1–4} However, current synthesis and derivatization of complex aziridines often involve lengthy functional group interconversion, tedious synthesis of exotic nitrene-equivalent reagents, and expensive transition metal catalysts.^{5,6} Due to the ubiquitous accessibility of amino alcohol derivatives from amino acids, peptides and biochemical feedstocks, it is conceivably desired to develop direct alcohol amination/cyclization methods to afford nitrogen-containing saturated heterocycles from the corresponding amino alcohol substrates. In addition, it can be synthetically advantageous if the native chirality in natural amino acids can be leveraged to access chiral nitrogen-heterocycles through stereospecific alcohol amination.

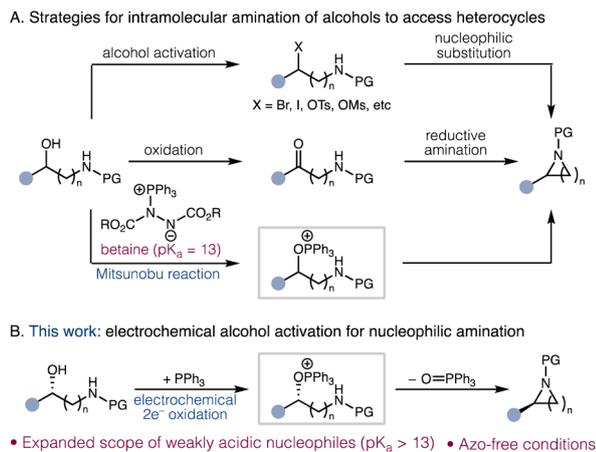
In spite of the abundance of the alcohol functionality,⁷ its use in direct amination reaction is scarce, considering the $-\text{OH}$ group is a poor leaving group in nucleophilic substitution reactions. To achieve effective functionalization, additional synthetic steps are often required to convert the alcohol to a better leaving group, such as an alkyl halide or sulfonate

ester,^{8,9} or a more reactive electrophile, for instance, an aldehyde or ketone, that can participate in reductive amination reactions with amine nucleophiles (Scheme 1A).^{10,11} Both approaches suffer from the multi-step functional group transformation and redox state interconversion. Although catalytic alcohol amination strategies are available *via* cascade alcohol oxidation and reductive amination,^{12,13} it is challenging to retain the chirality from the alcohol substrate *via* stereospecific amination due to the chirality loss in the alcohol oxidation step. Indeed, chiral catalysts are required for asymmetric hydrogenation of the imine intermediate.¹⁴ In contrast, the Mitsunobu reaction is synthetically attractive due to its single-step and stereochemically inverted alcohol substitution selectivity.^{15,16} Despite the continuous progress in improving its applicability and sustainability,^{17,18} the classic Mitsunobu reaction still suffers from two major limitations. First, only acidic nucleophiles ($\text{p}K_{\text{a}} < 13$) are effective, because it is critical for the nucleophile to protonate the zwitterionic betaine intermediate (Scheme 1A) and prevent its reaction with the alkoxyphosphonium cation species.¹⁹ For example, carboxylamides or aliphatic amines are not acidic enough to be employed as nucleophiles under the Mitsunobu reaction conditions. Moreover, the use of stoichiometric oxidants—azodicarboxylate esters—and the resulting hydrazine byproducts can lead to potential safety concerns and cumbersome purification in large-scale production.²⁰ Notably, during the preparation of this manuscript, Charette and coworkers reported a general strategy to employ weakly acidic nucleophiles in the Mitsunobu reaction by using a pre-made protonated betaine-like intermediate.²¹

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Scheme 1 Strategies for cyclization of amino alcohol substrates and synthesis of nitrogen heterocycles.

By taking advantage of the stereospecificity of the Mitsunobu reaction, we aimed to develop an electrochemical synthesis of chiral nitrogen heterocycles from accessible chiral amino alcohol building blocks (Scheme 1B). We hypothesized that the proposed transformation would overcome several challenges related to the azo-reagents in the classic Mitsunobu reaction by replacing the problematic azodicarboxylate chemical oxidants with anodic oxidation, inspired by our recent discovery of an electrochemical alcohol cyanation method and previously reported analogous stepwise electrosynthesis.^{22,23} Since the alkoxyphosphonium species is directly synthesized from anodic oxidation, bypassing the betaine intermediate, we envisioned that the electrochemical alcohol substitution reaction can employ an expanded scope of weakly acidic nitrogen nucleophiles ($pK_a > 13$). Although similar stepwise or one-pot alcohol nucleophilic substitution/C–N bond formation has been previously reported with azide and azole nucleophiles,^{24–26} the intramolecular amination/heterocycle synthesis has not been demonstrated. Moreover, experimental evidence and mechanistic studies of the proposed two-electron oxidation of phosphine and alcohol to yield the alkoxyphosphonium cation are also not available. Herein, we report electrochemical conditions for azo-free Mitsunobu-type synthesis of aziridine, pyrrolidine, oxazoline and related nitrogen heterocycles. Furthermore, cyclic voltammetry (CV) and linear sweep voltammetry (LSV) experiments provided proof of the proposed anodic two-electron oxidation mechanism leading to the alkoxyphosphonium intermediate.

Our optimization efforts started from studying the electrochemical cyclization of *N*-(2-hydroxyethyl)-toluenesulfonamide (**1**) to produce the corresponding aziridine **2** (Table 1). Initial constant current (10 mA) electrolysis of **1** in the presence of PPh_3 (1.2 equiv.), DBU base (1,8-diazabicyclo[5.4.0]undec-7-ene, 2.0 equiv.), tetrabutylammonium hexafluorophosphate (nBu_4NPF_6) supporting electrolyte (0.1 M), a reticulated vitreous carbon (RVC) anode and a nickel foam cathode yielded **2** with 14% yield (entry 1). Drastically increased yields were observed

with an acidic alcohol additive, HFIP (1,1,1,3,3,3-hexafluoroisopropanol), presumably due to the more favorable cathodic hydrogen evolution reaction (HER) (entries 2–4). The highest yield of 71% was achieved with 4.0 equiv. of HFIP. We hypothesize that the acidic but non-nucleophilic HFIP can accelerate the cathodic hydrogen evolution reaction (HER) without trapping the anodically generated phosphine radical cation.²⁷ Indeed, less hindered trifluoroethanol (TFE) and less acidic tert-butanol do not improve the aziridination reaction (entries 5 and 6). Besides DBU, other $N(sp^2)$ -centered organic bases, such as TBD (1,5,7-triazabicyclo[4.4.0]dec-5-ene), DMAP (4-(dimethylamino)pyridine) and 1,3,5-collidine, are also effective in promoting electrochemical alcohol amination (entries 7–9). In contrast, no product was observed when DBU was replaced by inorganic carbonate or phosphate bases (entries 10 and 11), potentially owing to their poor solubility in dichloromethane (CH_2Cl_2) solvent. Decreased yields were obtained when the electrolysis current was reduced to 2.5 and 5 mA, or increased to 12.5 mA (entries 12–14), presumably due to the different electrode potentials (see ESI, Fig. S13†) that can favor undesired redox events of DBU or CH_2Cl_2 solvent. Furthermore, control experiments lacking phosphine or electrolysis failed to produce any product (entries 15 and 16).

Table 1 Survey of electrolysis conditions^a

Entry	Base	Additive	Yield ^b of 2 (%)
1	DBU	—	14
2	DBU	HFIP (1.0 equiv.)	27
3	DBU	HFIP (3.0 equiv.)	37
4	DBU	HFIP (4.0 equiv.)	71
5	DBU	TFE (4.0 equiv.)	18
6	DBU	<i>t</i> -BuOH (4.0 equiv.)	12
7	TBD	HFIP (4.0 equiv.)	51
8	DMAP	HFIP (4.0 equiv.)	68
9	Collidine	HFIP (4.0 equiv.)	60
10	CS_2CO_3	HFIP (4.0 equiv.)	0
11	K_3PO_4	HFIP (4.0 equiv.)	0
12 ^c	DBU	HFIP (4.0 equiv.)	23
13 ^d	DBU	HFIP (4.0 equiv.)	36
14 ^e	DBU	HFIP (4.0 equiv.)	46
15 ^f	DBU	HFIP (4.0 equiv.)	0
16 ^g	DBU	HFIP (4.0 equiv.)	0

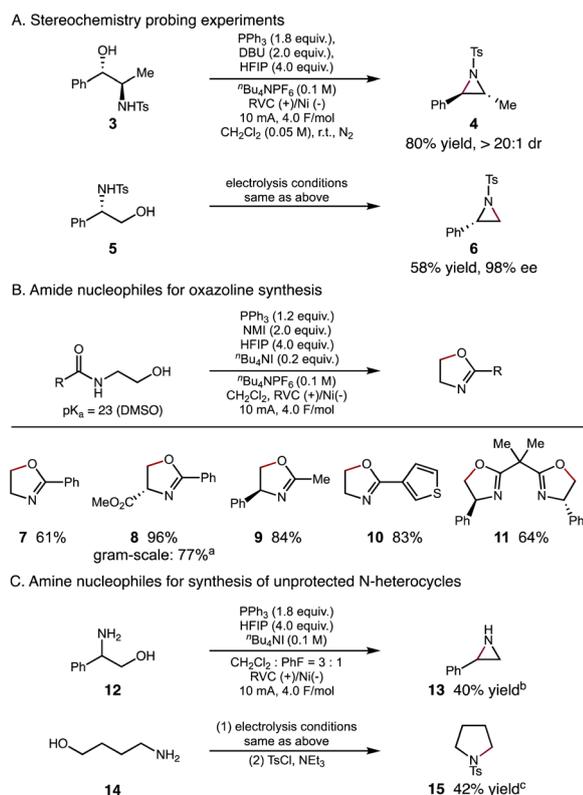
^a All reactions were performed at room temperature on a 0.25 mmol scale under a N_2 atmosphere. ^b Yields of product **2** were determined by ¹H-NMR with 1,3,5-trimethoxybenzene as the internal standard. ^c Electrolysis current $I = 2.5$ mA. ^d Electrolysis current $I = 5.0$ mA. ^e Electrolysis current $I = 12.5$ mA. ^f No PPh_3 is added. ^g No electrolysis.



Attempting to probe the stereospecificity of the alcohol nucleophilic amination, we applied the optimized conditions to the diastereotopic ephedrine-derived substrate **3**, which yielded the α -OH chiral carbon-center inverted aziridine product **4** with >20:1 diastereomeric ratio (d.r.) and 80% isolated yield (Scheme 2A). In comparison, the α -NHTs chiral carbon centers in **3** and **5** were retained in products **4** and **6** after electrolysis, consistent with a Mitsunobu-like S_N2 nucleophilic substitution mechanism. Moreover, we tested our hypothesis of employing weakly acidic nucleophiles, such as amines and amides, in the electrochemical Mitsunobu reaction by replacing the sulfonamide nucleophile with benzamide protecting groups ($pK_a = 23$ in DMSO).²⁸ Gratifyingly, by implementing slightly modified conditions including an NMI (*N*-methylimidazole) base and a ^tBu₄N⁺I⁻ catalyst, the oxazoline nucleophilic substitution products **7** and **8** were obtained in 61% and 96% yields, respectively, from the ethanolamine and serine-derived benzamide substrates, in which the O-atom in the amide moiety served as the nucleophilic site (Scheme 2B). Besides the benzamide protecting group, aliphatic and heterocyclic carboxylic acid-derived amides can also be employed to yield the corresponding oxazoline products efficiently (**9**, **10**). In addition, electrolysis of the 2,2-dimethylmalonamide substrate produced the chiral symmetric bis(oxazoline) (BOX) chiral ligand in 64% yield under the standard conditions. Ostensibly, electrolysis of

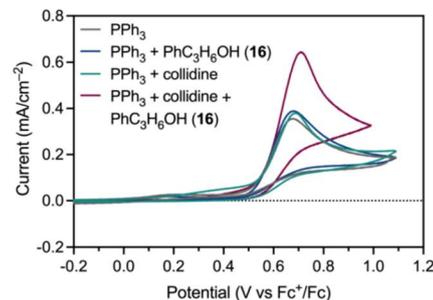
unprotected amino alcohols (**12**, **14**) ($pK_a(\text{NH}_3) = 41$ in DMSO)²⁹ also yielded the corresponding free aziridine (**13**) and pyrrolidine (**15**) products in moderate yields (Scheme 2C). The same electrochemical conditions can be adapted for large-scale synthesis, as gram-scale batch electrolysis successfully yielded 77% yield of **8**. These collective observations successfully corroborated the hypothesis that the pK_a limit in the classic Mitsunobu reaction can be alleviated by replacing the azo chemical oxidants with anodic oxidation of phosphine and alcohol, affording the critical alkoxyphosphonium cation and the nucleophilic substitution product without the betaine intermediate.

To further investigate the proposed two-electron anodic oxidation mechanism of phosphine and alcohol, cyclic voltammetry experiments were used to probe their redox properties in CH₂Cl₂ solvent on a glassy carbon electrode (Scheme 3A). Consistent with our previous electrochemical cyanation report,²² PPh₃ exhibited a fully irreversible oxidation peak with

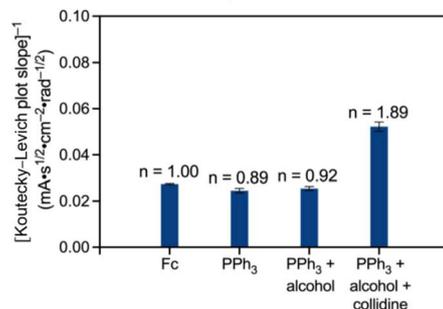


Scheme 2 Stereochemistry and nucleophile scope. ^a8.0 mmol scale reaction with 1.8 eq. of PPh₃ and 5.0 F mol⁻¹ charge. ^bNMR yield was used. ^cTosyl protection was conducted after electrolysis to quantify the product yield more accurately with ¹H-NMR.

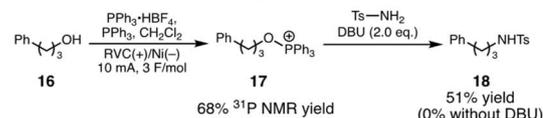
A. Cyclic voltammograms of PPh₃, alcohol and collidine base



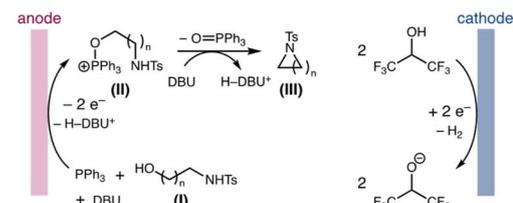
B. Electron transfer stoichiometry



C. Nucleophilic substitution of alkoxyphosphonium



D. Proposed mechanism



Scheme 3 Electrochemical mechanistic studies and proposed reaction mechanism.

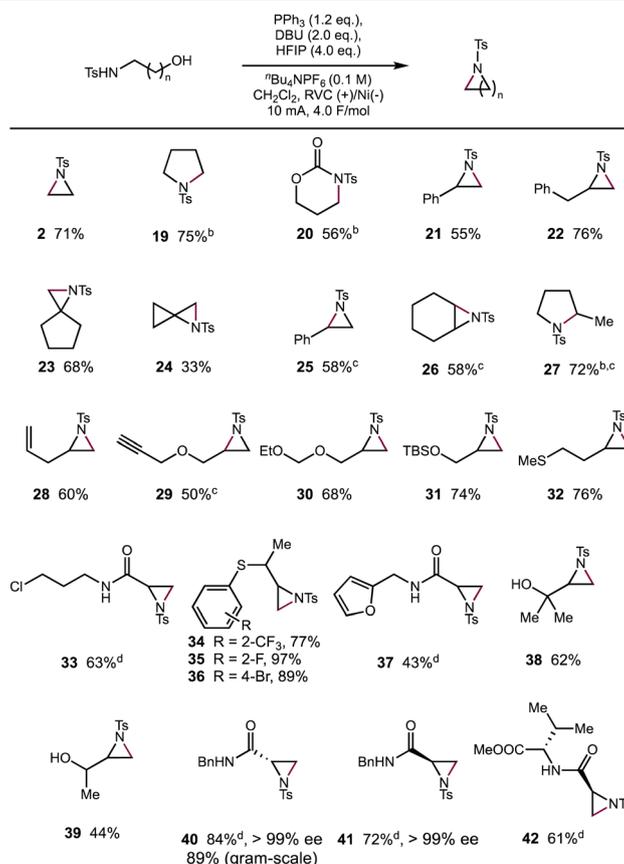


the onset close to its oxidation potential ($E(\text{PPh}_3^{+}/\text{PPh}_3) = 0.54$ V vs. Fc^+/Fc). This irreversibility is potentially resulting from facile side reactions of PPh_3^{+} with solvent and residual moisture. Inclusion of alcohol **16** and 1,3,5-collidine base separately showed negligible changes in the PPh_3 cyclic voltammogram. The collidine base was chosen for the electrochemical mechanistic studies because the DBU base exhibited noticeable background oxidation current interfering with the $\text{PPh}_3^{+}/\text{PPh}_3$ redox couple (see ESI, Fig. S3[†]). Notably, when both alcohol **16** and 1,3,5-collidine were added, a significant enhancement of the PPh_3 oxidation peak current was observed, indicating an increased electron transfer stoichiometry in the electrochemical oxidation. To further investigate the mechanism of the anodic oxidation observed in cyclic voltammetry, linear sweep voltammetry (LSV) on a glassy carbon rotating-disc electrode (RDE) was used to extract the electron transfer stoichiometry of PPh_3 oxidation with the alcohol substrate and collidine base. By comparing the Koutecký–Levich plot³⁰ slopes of PPh_3 with that of ferrocene (Fc), anodic oxidation of PPh_3 with and without alcohol **16** was dominated by single-electron transfer (Scheme 3B, also see ESI, Section S4[†]). In contrast, the electrochemical oxidation of PPh_3 in the presence of both alcohol **16** and 1,3,5-collidine is mostly dictated by a two-electron oxidation pathway

(see ESI, Section S4.4[†]), consistent with the proposed deprotonative oxidation mechanism to yield the alkoxyphosphonium cation intermediate (Scheme 1B). By adapting previously reported electrolysis conditions,²⁴ we have prepared and characterized alkoxyphosphonium **17** with 68% ³¹P-NMR yield, which successfully converted to the intermolecular nucleophilic substitution sulfonamide product **18** in 51% yield when treated with the TsNH_2 nucleophile and DBU base (Scheme 3C, also see ESI, Section S7[†]). The TsNH_2 ($\text{p}K_a = 16.3$)³¹ nucleophilic substitution of alkoxyphosphonium failed to yield any product without DBU ($\text{p}K_a = 13.9$),³² indicating that the deprotonated sulfonamide anion is the effective nucleophile, although the deprotonation is thermodynamically disfavored.

Combining voltammetry and stoichiometric trapping of the alkoxyphosphonium cation, the reaction mechanism is proposed in Scheme 3D. Anodic two-electron oxidation and deprotonation of phosphine and the amino alcohol substrate (**I**) yielded the alkoxyphosphonium cation (**II**), followed by an intramolecular nucleophilic substitution by the amine/amide nucleophiles, affording the desired heterocyclic product (**III**). Cathodic proton reduction-hydrogen evolution from HFIP furnishes the entire electrochemical circuit. Thermodynamically favorable proton transfer from protonated H-DBU^+ ($\text{p}K_a =$

Table 2 Survey of various amino alcohol substrates^a



^a Reactions were run on a 0.5 mmol scale. Yields are for isolated material following chromatography on silica gel unless otherwise noted. ^b Reaction was refluxed. ^c 4-Dimethylaminopyridine (DMAP) used as a base, with $n\text{Bu}_4\text{NI}$ (0.2^{eq.}) added. ^d *N*-Methylimidazole (NMI) used as a base.



13.9) to the HFIP-derived alkoxide anion ($pK_a(\text{HFIP}) = 17.9$)³³ can regenerate the DBU base and HFIP alcohol. Initial reaction kinetics under the optimized electrolysis conditions were measured to be $(8.07 \pm 0.27) \times 10^{-4} \text{ mmol min}^{-1}$ (see ESI, Fig. S14†), which corresponds to a faradaic yield of $(26 \pm 1)\%$. It is also noteworthy that a gradual rate increase was observed as the electrolysis progresses, presumably due to the accumulation of the alkoxyphosphonium intermediate and accelerated nucleophilic substitution by the sulfonamide nucleophile. The anodic oxidation potential under the optimized bulk electrolysis conditions was also measured in the presence of a Ag^+/Ag reference electrode to be around 3.6 V vs. Fc^+/Fc (see ESI, Fig. S12†). This large overpotential compared to the $\text{PPh}_3^{+}/\text{PPh}_3$ couple is likely due to the sluggish electron transfer kinetics and substantial mass transfer resistance in relatively non-polar dichloromethane solvent.

Lastly, we examined the scope of different amino alcohol substrates in the electrochemical cyclization/nucleophilic substitution reaction (Table 2). Consistent with the small-scale optimization experiments, aziridine **2** was obtained in 71% isolated yield from the optimized electrolysis conditions. Besides aziridines, pyrrolidine (**19**) and six-membered carbamate (**20**) can also be synthesized in 75% and 56% yields from the corresponding 4-amino-1-butanol-derived sulfonamide and 1,3-diol-derived carbamate substrates, respectively. The latter can be synthetically useful in synthesizing 1,3-aminoalcohols from the corresponding 1,3-diol substrates. In addition, phenyl (**21**), benzyl (**22**) and spiro- (**23**, **24**) aziridines can be successfully accessed from electrolysis in good to moderate yields. Substrates containing secondary alcohols (**25–27**) are also suitable under the optimized conditions, affording the substituted mono- and bicyclic aziridine and pyrrolidine products with good efficiencies. Gratifyingly, a broad range of functional groups can be tolerated under the electrolysis conditions, including alkenes (**28**), alkynes (**29**), acetals (**30**), silyl ethers (**31**), thioethers (**32**) and alkyl halides (**33**). Moreover, substrates containing electron-deficient arenes (**34–36**) and electron-rich heterocycles (**37**) also yielded the corresponding aziridine products in satisfactory yields. The sulfide (**32**, **34–36**) and furan-containing (**37**) examples are particularly noteworthy because it is well known that furan and sulfides can be readily oxidized to the corresponding polyfuran,³⁴ sulfoxide or sulfone compounds,³⁵ indicating mild and selective anodic oxidation under the optimized conditions. For substrates containing more than one alcohol moiety (**38**, **39**), the cyclization is chemoselective for primary alcohols, presumably controlled by steric hindrance in trapping the electrochemically generated PPh_3^{+} species. Gratifyingly, by substituting the DBU base under optimized conditions with the milder NMI base ($pK_a(\text{H-NMI}^+) = 6.4$),³⁶ chiral aziridine carboxylamides can be synthesized from accessible (L)- and (D)-serine derivatives (**40**, **41**) and dipeptides (**42**) with no noticeable racemization, elucidating potential applications in biorthogonal functionalization and modification of peptides. To demonstrate the synthetic potential of the electrochemical aziridination reaction, gram-scale synthesis of **40** was conducted under the same conditions with 89% yield.

Conclusions

In conclusion, we developed an electrochemical alcohol nucleophilic substitution method for the synthesis of aziridines and other nitrogen heterocycles. Voltammetry studies confirmed the two-electron oxidation mechanism of phosphine and alcohol to generate the alkoxyphosphonium intermediate, followed by facile nucleophilic substitution by sulfonamides for the synthesis of various nitrogen heterocycles. The electrochemical substitution method also accepts weakly acidic amide and amine nucleophiles. This work demonstrates the potential of employing electrochemistry for azo-free Mitsunobu-type alcohol substitution with both improved practicality and expanded synthetic scope.

Data availability

The data supporting this article have been included as part of the ESI.†

Author contributions

E. A. Hale and Q. Zhu conceived and designed the project. E. A. Hale carried out the synthesis and catalytic experiments. E. A. Hale and Q. Zhu conducted the electroanalytical mechanistic studies. E. A. Hale and Q. Zhu contributed to the interpretation of the results and the preparation of the manuscript.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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