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A general, electrocatalytic approach to the synthesis of vicinal diamines

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This protocol describes an electrochemical synthesis of 1,2-diazides from alkenes. Organic azides are highly versatile intermediates for synthetic chemistry, materials, and biological applications. 1,2-Diazides are commonly reduced to form 1,2-diamines, which are prevalent structural motifs in bioactive natural products, therapeutic agents, and molecular catalysts. The electrochemical formation of 1,2-diazides involves the anodic generation of an azidyl radical from sodium azide, followed by two successive additions of this N-centered radical to the alkene, and is assisted by a Mn catalyst. The electrosynthesis of 1,2-diazides can be carried out using various experimental setups comprising custom-made or commercially available reaction vessels and a direct-current power supply. Readily accessible electrode materials can be used, including carbon (made from reticulated vitreous carbon and pencil lead), nickel foam, and platinum foil. This protocol is also demonstrated using ElectraSyn, a standardized electrochemistry kit. Compared with conventional synthetic approaches, electrochemistry allows for the precise control of the anodic potential input, eliminates the need for stoichiometric and often indiscriminate oxidants, and minimizes the generation of wasteful byproducts. As such, our electrocatalytic synthesis exhibits various advantages over existing methods for alkene diamination, including sustainability, operational simplicity, substrate generality, and exceptional functional-group compatibility. The resultant 1,2-diazides can be smoothly reduced to 1,2-diamines in a single step with high chemoselectivity. To exemplify this, we include a procedure for catalytic hydrogenation using palladium on carbon. This protocol, therefore, constitutes a general approach to accessing 1,2-diazides and 1,2-diamines from alkenes.

Introduction

The carbon–nitrogen (C–N) bond is a ubiquitous structural motif in bioactive natural products, synthetic pharmaceuticals, and molecular catalysts[1]. Indeed, >90% of the 100 top-selling small-molecule drugs in the United States in 2016 had one or more C–N bonds[2]. In particular, 1,2-diamines are frequently found in bioactive natural products, therapeutic agents, and molecular catalysts (Fig. 1)[3]. A particularly powerful approach to their preparation is the direct addition of two nitrogen-based functional groups (FGs) to alkenes[4], because alkenes are abundant, readily accessible, and structurally diverse feedstocks. Although there are already a number of methods for achieving this, better general and selective approaches to the diamination of alkenes are still desirable.

Synthetic electrochemistry offers a mild and efficient alternative to conventional chemical approaches for transformations involving redox processes[5–7]. With electricity as the 'reagent' instead of chemical oxidants or reductants, organic starting materials can lose or gain electrons at the electrode surface to produce reactive intermediates, and the rate and chemoselectivity of this process can be controlled precisely and externally by regulating the applied potential or current. Thus, electrochemistry constitutes an inherently selective and sustainable method for the functionalization of organic molecules. Indeed, electrochemistry has been used for C–N-bond-forming reactions such as aromatic C–H amination[8] and alkene aziridination[9].

In this protocol, we describe a Mn-catalyzed electrochemical approach for the synthesis of 1,2-diazides and 1,2-diamines from alkenes that uses sodium azide as the N source (Fig. 2a)[10]. The integration of electrochemistry and catalysis[11] allows for the synergistic control of both the generation and the downstream reactions of highly reactive radical intermediates.

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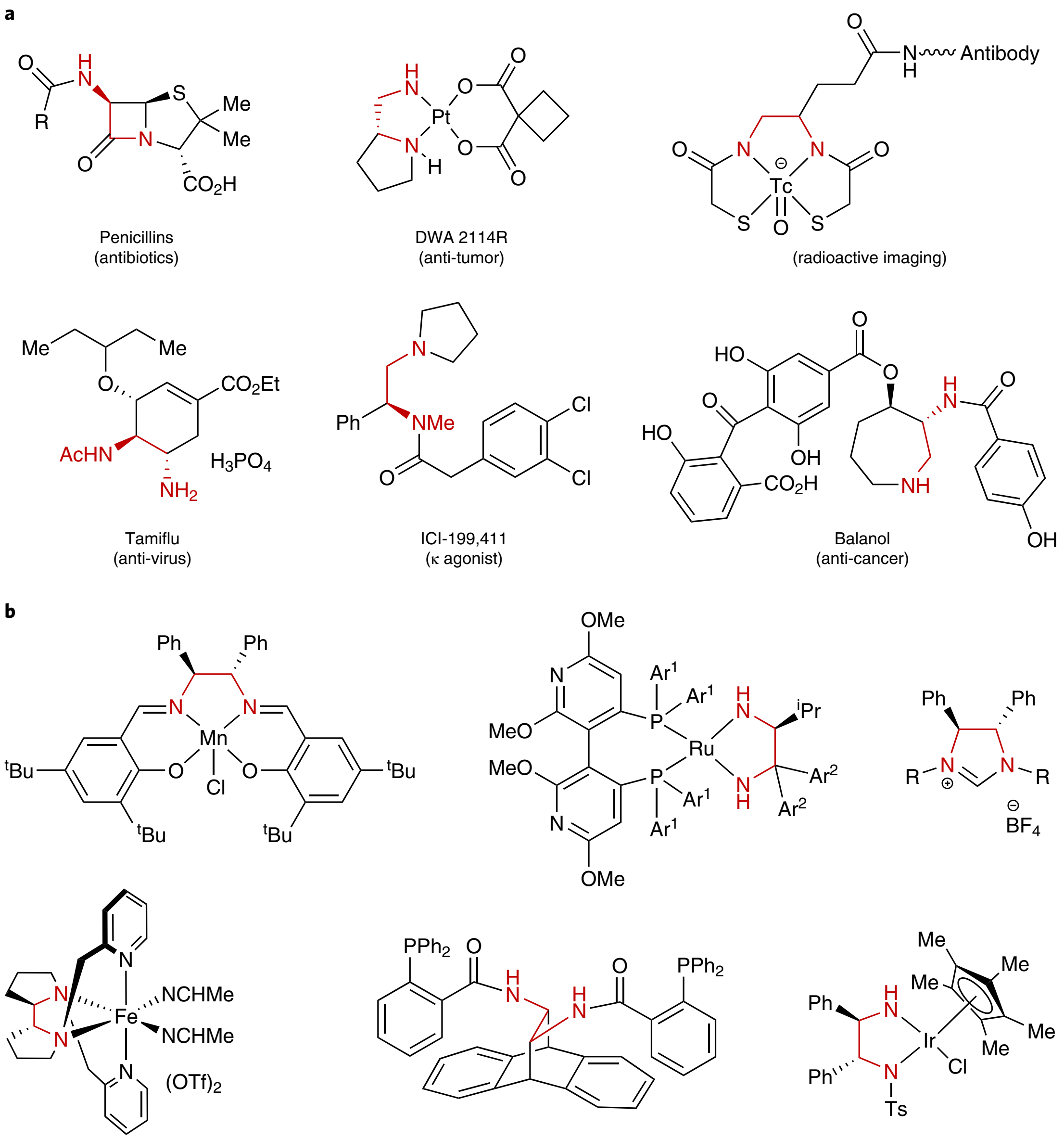
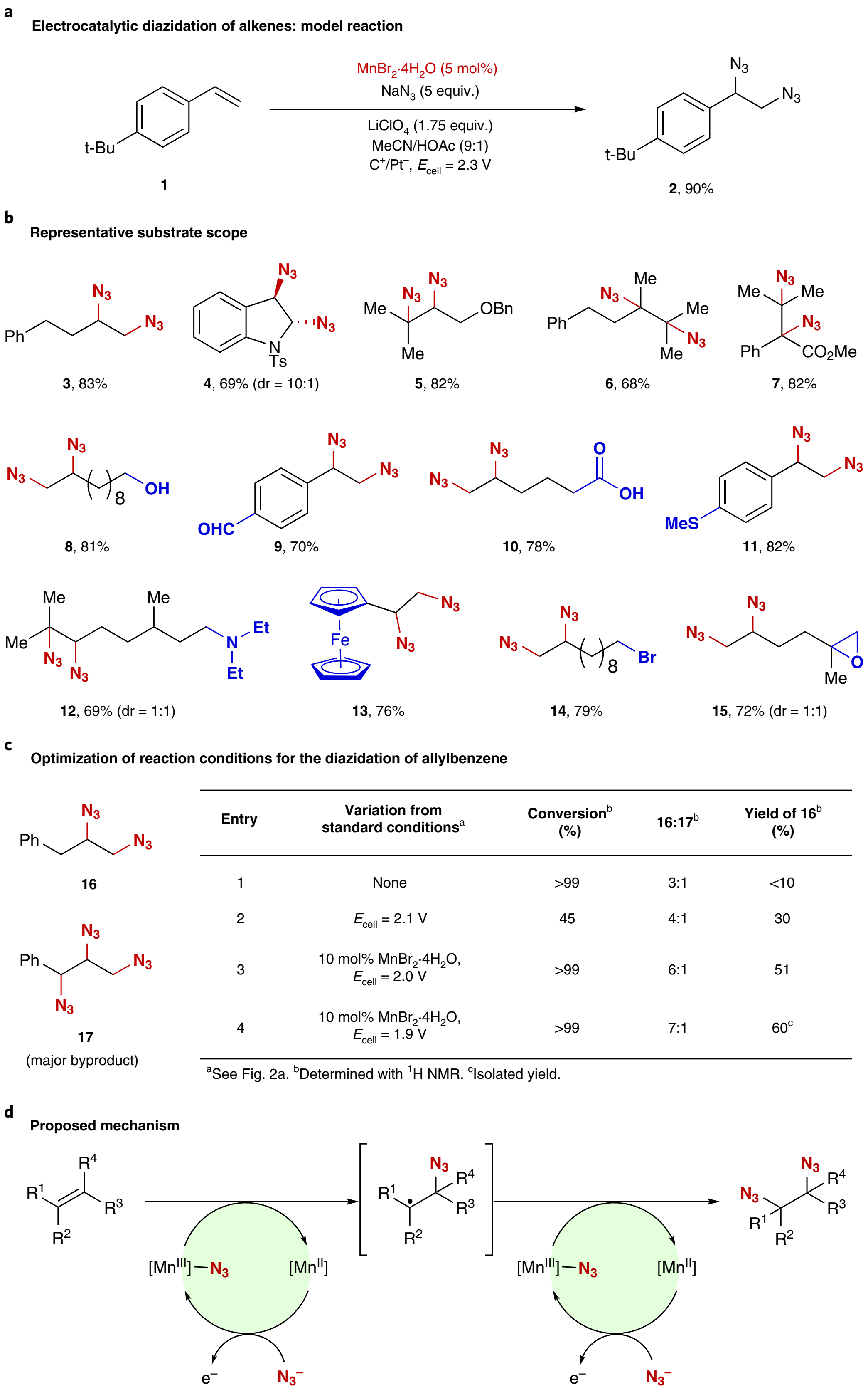


Fig. 1 | Importance of 1,2-diamines in synthetic and medicinal chemistry a,**b**, Medicinally relevant compounds (**a**) and synthetic catalysts (**b**) containing 1,2-diamine motifs (highlighted in red).

Mechanism and scope of the Mn-catalyzed electrochemical approach

The electrochemical diazidation uses an earth-abundant, inexpensive, and low-toxicity manganese catalyst. A proposed mechanism for this reaction is shown in Fig. 2d. The Mn catalyst has two primary roles: (i) it lowers the potential needed to oxidize N_3^- to the azidyl radical equivalent in the form of $[Mn^{III}]–N_3$, and (ii) it promotes the chemoselective addition of the azidyl radical group first to the alkene and then to the incipient carbon-centered radical to complete the diazidation. This catalytic effect, in combination with the granular control over the applied oxidizing potential enabled by electrochemistry, allows the radical reaction to occur under very mild conditions, which provides some explanation for the broad substrate scope and high FG compatibility of this approach, as compared with other methods for alkene diamination. Alkenes with any substitution pattern (**3**–**15**) are suitable substrates, including tetrasubstituted alkenes (**6** and **7**), for which few previous diamination protocols are available[12]. Moreover, oxidatively sensitive FGs such as alcohols (**8**), aldehydes (**9**), carboxylic acids (**10**), enolizable ketones, sulfides (**11**), amines (**12**), and ferrocenes (**13**) are compatible with our method (Fig. 2b). Current methods[13–22] cannot accommodate the majority of these functionalities, and therefore, our protocol provides access to medicinally relevant molecules that are otherwise challenging to synthesize. The conditions and scope of five representative existing



Entry	Variation from standard conditions[a]	Conversion[b] (%)	16:17[b]	Yield of 16[b] (%)
1	None	>99	3:1	<10
2	E_{cell} = 2.1 V	45	4:1	30
3	10 mol% MnBr$_2$·4H$_2$O, E_{cell} = 2.0 V	>99	6:1	51
4	10 mol% MnBr$_2$·4H$_2$O, E_{cell} = 1.9 V	>99	7:1	60[c]

[a]See Fig. 2a. [b]Determined with ^{1}H NMR. [c]Isolated yield.

Fig. 2 | Electrocatalytic diazidation of alkenes. a–**d**, model reaction (**a**), representative substrate scope (**b**), optimization of reaction conditions for the diazidation of allylbenzene (**c**), and proposed mechanism (**d**). dr, diastereomeric ratio.

methods are given in Table 1, so that interested readers may choose the approach to adopt according to the desired product structure and availability of reagents.

Adapting the example shown in the Procedure to the synthesis of other diazides

Although the reported protocol is demonstrated for the synthesis of 1-(*tert*-butyl)-4-(1,2-diazidoethyl)benzene (**2**), the same system can be easily adapted for the diazidation of a myriad of other alkene substrates (Fig. 2b) with minimal, if any, procedural modification. For relatively inert substrates, such as monosubstituted aliphatic alkenes (**3**, **8**, **10**, **14**, **15**) and electron-deficient alkenes (**7**, **12** (we hypothesize that the reactivity of the C=C bond in **12** is attenuated by the protonation of the tertiary amino group.)), increasing the reaction temperature to 40 °C or the catalyst loading to 10 mol%, or both, can resolve the reactivity issue and improve the yield of the corresponding 1,2-diazide in most cases. The changes to the procedure that are required for these substrates are given in 'Anticipated results' section. When carrying out the protocol with these substrates, monitoring the reaction via thin-layer chromatography is the most effective way to determine the progress and achieve high yield. However, once a steady current is observed, the theoretical reaction time can also be estimated based on the time necessary at that current to pass 2 F/mol of charge. For example, following the steps in section 1, using 1-(*t*-butyl)-4-vinylbenzene as the substrate, the observed current is typically 5–8 mA, meaning 2 F of current will typically pass in 80–130 min.

Limitations of the approach

We note that at the current stage, our synthetic protocol does not allow for the direct access to enantiomerically pure 1,2-diazides and 1,2-diamines. However, the racemic mixture of many 1,2-diamines can be readily resolved using a chiral reagent (e.g., tartaric acid) to produce the enantiomers in high purity[23]. This electrosynthetic method has not yet been successfully applied to the following classes of substrates: (i) alkenes containing FGs that are more easily oxidized than the catalyst (e.g., 4-vinylaniline and 4-vinylphenol), (ii) highly electron-deficient alkenes such as acrylates (however, styrene-derived acrylates such as **7** are suitable substrates), and (iii) alkenes bearing highly labile C–H bonds (e.g., *N*-Boc-1,4-dihydropyrrole and 1,4-dihydronaphthylene) because of competing C–H abstraction by the azidyl radical (N_3). For some substrates in the third category, rational optimization of the reaction conditions can minimize the aforementioned side reactions and allow the corresponding 1,2-diazides to be obtained in a synthetically useful yield. We exemplify the optimization logic with the diazidation of allylbenzene (Fig. 2c). This substrate contains an unactivated terminal alkene and labile benzylic/allylic C–H bonds that can undergo competing side reactions via H atom abstraction by N_3. Under the standard reaction conditions (Fig. 2a), only traces of the desired product **16** were observed in concomitance with a variety of by-products including **17** (entry 1). Lowering the cell voltage from 2.3 to 2.1 V, however, increased the yield of **16**, presumably owing to suppression of the anodic generation of free azidyl radical from N_3^- (entry 2). Improving the catalyst loading and further decreasing the cell voltage proved effective in promoting the conversion of allylbenzene to 1,2-diazide in good yield and high chemoselectivity. (For modified protocol, see 'Anticipated results'.)

Experimental considerations

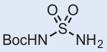
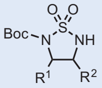
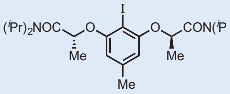
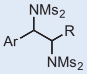
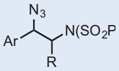
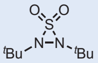
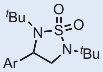
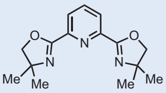
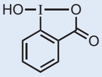
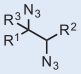
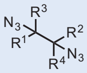
Equipment setup

From an operational perspective, the reaction protocol can be readily executed using common laboratory glassware, commercial electrodes, and a direct-current power supply. In particular, the 1,2-diazide synthesis has been demonstrated with ElectraSyn—a compact electrochemistry kit recently developed by Baran and colleagues[24] to streamline synthetic electrochemistry (Box 1). The purification step is straightforward and often requires only an aqueous workup or the passage of the crude reaction mixture through a short silica plug. The required reagents (sodium azide, lithium perchlorate, and manganese(II) bromide) are commercially available and inexpensive. Electricity is the sole energy source, and H_2 and sodium acetate constitute the only by-products.

Safety considerations

Many organic azides are sensitive to thermal and mechanical impacts. We analyzed the thermal decomposition properties of the synthetic intermediates, 1,2-diazides, using thermogravimetric analysis (TGA), as such information is important to developing safe chemical processes for their large-scale preparation

Table 1 | Comparison of representative existing methods for alkene diamination with current protocol

Ref.	Catalyst	N source	Oxidant	Substrate scope	FG compatibility	Product structure
Olson et al.[15]	$Rh_2(esp)_2$ (2 mol%)	 $BocHNSO_2NH_2$	$PhI(OAc)_2$ (1.2 equiv.)	Mono- and 1,2-di-substituted alkenes	Oxidation-sensitive (FGs not explored	
Muñiz et al.[16]		Ms_2NH (2.5 equiv., 1.25 equiv. per C–N bond)	*m*CPBA (2 equiv.)	Styrenes (mono- and 1,2-di-substituted)	Oxidation-sensitive FGs not explored	
Zhang and Studer[17]	CuCl (5 mol%), phenanthroline (5 mol%)	$TMSN_3$ (1.5 equiv.), $(PhSO_2)_2NF$ (1.5 equiv.)	Same as the N source	Styrenes (mono- and di-substituted)	Oxidation- or nucleophilic substitution-sensitive FGs not explored	
Zhao et al.[18]	CuCl (10–20 mol%), PBu_3 (10–20 mol%)		Same as the N source	Styrenes (mono-substituted), vinyl ethers	Oxidation-sensitive FGs not explored	
Yuan et al.[19]	$Fe(OTf)_2$ or $Fe(NTf_2)_2$ (1–10 mol%), 	$TMSN_3$ (3.6–4 equiv., 1.8–2 equiv. per C–N)		Mono-, di-, and tri-substituted alkenes	Oxidation- or nucleophilic substitution-sensitive FGs not explored	
The current protocol	$MnBr_2·4H_2O$ (5–10 mol%)	NaN_3 (5 equiv., 2.5 equiv. per C–N bond)	None	Mono-, di-, tri-, and tetra-substituted alkenes	Compatible with a variety of FGs sensitive to oxidation or nucleophilic substitution	

(knowing the decomposition temperature allows process chemists to choose the temperature at which to run the reaction with low risk of accidents). The thermal stability of various 1,2-diazides has also been examined in a previous report, using differential scanning calorimetry[25]. The lowest onset temperature for decomposition observed between this report and our own work was ~100 ºC, allowing for a convenient operating margin for practicing the diazide synthesis at room temperature (21–22 ºC). Although these organic azides are still potentially hazardous, their elaborate isolation is unnecessary, as the subsequent reduction to 1,2-diamines can be carried out in tandem with the diazidation with minimal intermediary workup.

Scale of the reaction

The electrocatalytic protocol is demonstrated on both 0.2 mmol and 3 mmol scales and will probably work on further-augmented scales. When scaling up the reaction, minimal procedural changes are required in addition to increasing the volume of the reaction vessel and the size of the electrodes, and maintaining a sufficient stirring rate. In addition, preparative scale reactions are better carried out using constant-current electrolysis (see ‘Experimental design’ section). Modification of these parameters was sufficient to optimize the 3 mmol scale reaction. From a safety perspective, it is important to take appropriate precautions when working with inorganic and organic azides, especially at scale[25]. All procedures should be performed in a well-ventilated fume hood to avoid exposure to hydrazoic acid, a side product of the reaction. Efforts to develop a safe and streamlined large-scale process for 1,2-diamine preparation are currently under way.

Experimental design

Electrocatalytic diazidation of alkenes: design, mechanism, and application

Our optimized reaction system for the electrocatalytic diazidation of alkenes comprises NaN_3 as the azide source, manganese(II) bromide as the catalyst, lithium perchlorate or tetrabutylammonium

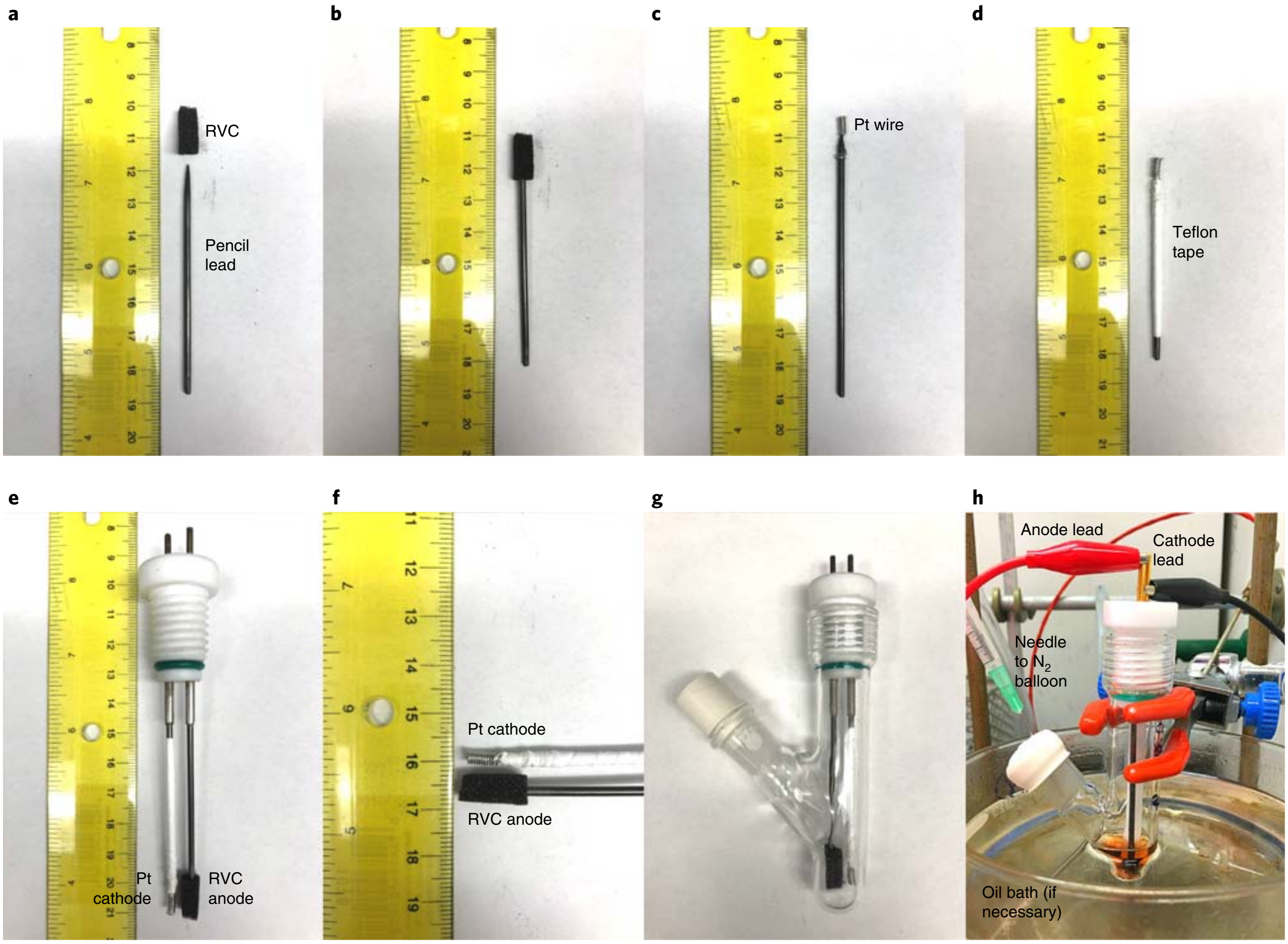


Fig. 3 | Electrolysis setup for 0.2 mmol scale reactions. a–h, Assemblies of the RVC anode (**a**,**b**), Pt cathode (**c**,**d**), the cap (**e**,**f**), and the whole electrochemical cell (**g**,**h**).

hexafluorophosphate as the electrolyte, acetic acid as the electron acceptor, and acetonitrile as the solvent. The hypothesized reaction pathway involves the Mn-mediated transfer of the azidyl radical to both the $C{=}C$ π-bond in the alkene substrate and the resultant carbon-centered radical (Fig. 2d), forming two $C–N_3$ bonds and producing the 1,2-diazide product[10]. The catalyst maintains the reaction selectivity toward the desired diazidation; without the catalyst, only traces of the 1,2-diazide are formed after full conversion of the alkene. The electrolyte is necessary to ensure sufficient ion conductivity of the reaction medium, which is required for electrochemistry. Acetic acid is used for the cathodic proton reduction to form H_2. This reduction occurs simultaneously with the desired anodic alkene functionalization to balance the charge of the solution and complete the circuit. All reactants and reagents are commercially available.

Reticular vitreous carbon, a commercially available, porous carbon electrode, is used as the anode material, owing to its accessibility and stability under oxidative conditions. Platinum is used as the cathode, owing to its highly catalytic efficiency in proton reduction and stability under reductive conditions. Nickel foam, a more economical material, has also been successfully used as the cathode instead of Pt for the reaction shown in Fig. 2a, with minimal influence on reaction efficiency (see the Supplementary Methods and Supplementary Fig. 1).

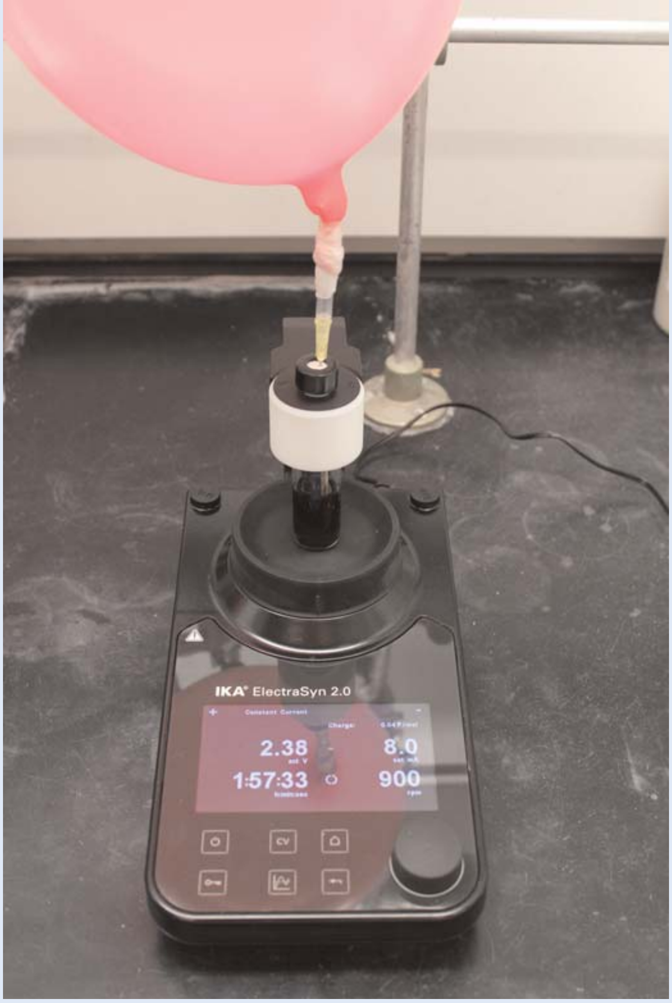
Recently, we have also applied this reaction design and experimental protocol for the electrocatalytic dichlorination[26] and halotrifluoromethylation[27] of alkenes.

Electrolysis setup

The electrocatalytic 1,2-diazide synthesis described herein has been carried out in our laboratory on scales ranging from 0.2 to 3 mmol. Further scale-up of the reaction is theoretically possible but has not

Box 1 | Diazidation procedure with ElectraSyn 2.0 (0.3 mmol scale) ● Timing 2.5 h

This protocol demonstrates the use of ElectraSyn, a commercial kit designed to simplify and standardize synthetic electrochemistry setup, for the diazidation of **1** to form **2**.



Additional materials

Balloon
Stir bar
Reticulated vitreous carbon (100 pores per inch; ERG Aerospace)
Nickel foam (MTI, cat. no. EQ-bcnf-16m)
Teflon tape (Black Swan, part no. 02090-10)
Syringes (1, 3, 6, and 12 mL)
Hypodermic needles (18, 20, and 22 gauge, 1.5 inch and 22 gauge, 3 inch)
Glass vials (1.5 dram and 20 mL)
Rotary evaporator
NMR spectrometer
ElectraSyn 2.0 (IKA, cat. no. 0020008980)
Graphite electrode assembly (IKA, cat. no. 0040002858)
Open-top screw cap (cap size: 15-425; VWR, cat. no. 66012-598)
Silicone/polytetrafluoroethylene (PTFE) septum (size: for 15-425 screw cap; Fisher, cat. no. 03-394A)

Procedure

Preparation of the electrodes ● Timing 2 min

1. Remove the graphite plate from the ElectraSyn graphite electrode assembly to obtain the empty electrode holder.
2. Cut a piece of reticulated vitreous carbon (RVC; 5.3 × 0.8 × 0.6 cm^3) and slot it in the empty electrode holder as the working electrode (Supplementary Fig. 2).
3. Cut two pieces of nickel foam (5.3 × 0.8 × 0.16 cm^3), stack them on top of each other, and slot them in the empty electrode holder as the counter electrode (Supplementary Fig. 2).

Box 1 | (continued)

Small-scale (0.3 mmol) synthesis ● Timing 2.5 h

4 Charge the ElectraSyn vial (10 mL volume) with a Teflon-coated magnetic stir bar, $MnBr_2{\cdot}4H_2O$ (4.2–4.3 mg, 0.015 mmol, 5 mol%), and NaN_3 (98.0 mg, 1.5 mmol, 5.0 equiv.).
5 Cover the screw thread area of the vial with a piece of Teflon tape (1.3 × 15 cm^2) to ensure that the seal is airtight (Supplementary Fig. 3).
6 Adapt the RVC and nickel foam electrodes to the ElectraSyn vial cap.
7 Screw the vial cap onto the vial to finger-tight (Supplementary Fig. 4).
8 Cap the reagent addition port of the ElectraSyn vial with an open-top screw cap adapted with a rubber septum.
9 Using a syringe, add electrolyte solution (6.0 mL, 0.1 mol/L $LiClO_4$ in CH_3CN) through the rubber septum.
10 Add 1-(*tert*-butyl)-4-vinylbenzene (55 µL, 48.0 mg, 0.3 mmol) to the ElectraSyn vial, followed by 0.6 mL of acetic acid.
11 Pierce the rubber septum with a long needle from the nitrogen inlet line and make sure the tip of the needle is in the solution. Pierce the rubber septum again with an additional needle to serve as a nitrogen vent.
12 Purge the mixture with nitrogen gas for ~3 min. No stirring is needed.
13 Remove both the inlet and outlet needles.
14 Pierce the rubber septum with a needle and connect to a nitrogen-filled balloon to sustain a nitrogen atmosphere.
15 Adapt the electrochemical cell to the ElectraSyn 2.0 vial holder (Supplementary Fig. 5).
16 Select ‘New experiments’ at ‘Constant voltage’.
17 Adjust the cell voltage to 2.3 V. Typically, a steady-state current of ~22 mA is observed.
18 Select ‘No’ for ‘Are you using a reference electrode’.
19 Adjust the reaction time to ‘2.0 hours’.
20 Adjust ‘mmols substrate’ to ‘0.3 mmol’.
21 Select ‘No’ for ‘Would you like to alternate the polarity’.
22 Review the parameters and start the experiment.
23 After electrolysis for 2 h, disconnect the reaction vial from the ElectraSyn 2.0, gently remove the cap with electrodes from the vial, and transfer the reaction medium to a separatory funnel. Wash both electrodes with ethyl acetate (10 mL) to transfer any residual product.
24 Add 20 mL of ethyl acetate to the separatory funnel and wash the organic solution with saturated aqueous $NaHCO_3$ (20 mL × 3).
25 Dry the organic layer with anhydrous sodium sulfate (~5.0 g) and decant it into a round-bottom flask.
26 Remove the solvent using a rotary evaporator.
27 Obtain an NMR measurement of the residue. The product appears spectroscopically pure, with a 94% yield.
? TROUBLESHOOTING

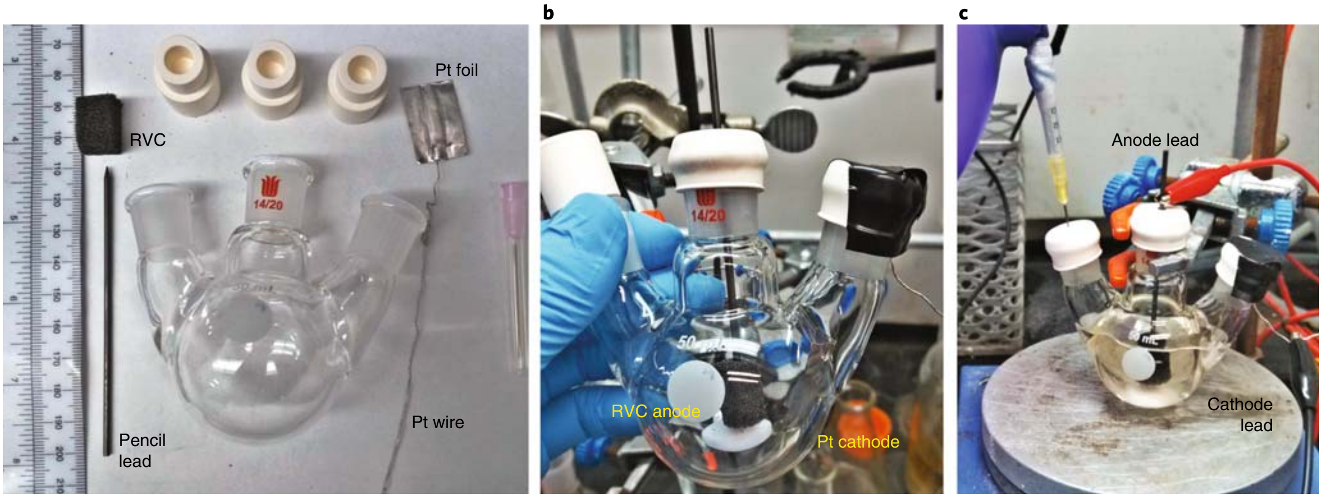


Fig. 4 | Electrolysis setup for 3 mmol scale reactions. Assemblies of the RVC anode and Pt cathode (**a**), and the whole electrochemical cell (**b**,**c**).

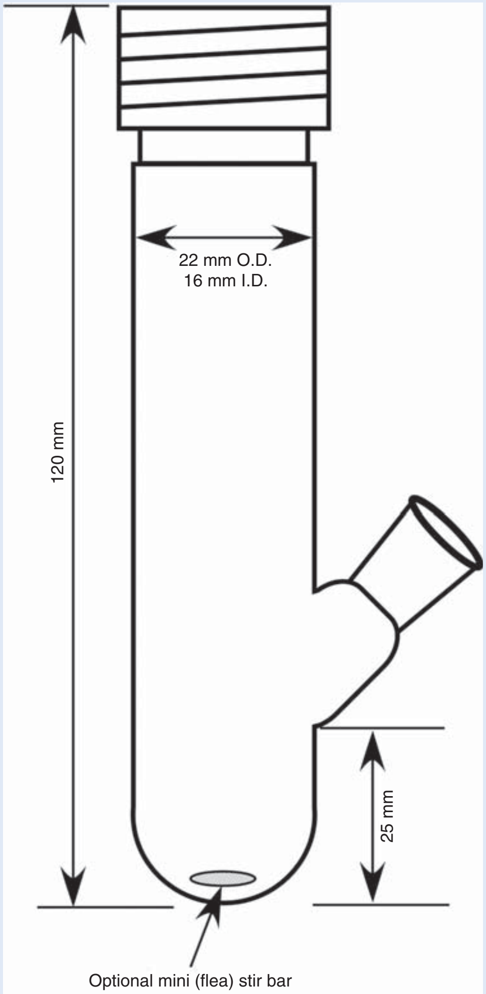
been executed in our laboratory. The electrolysis experiments have been conducted with three different setups using either commercially available or custom reaction vessels (Box 1 and Figs. 3 and 4).

The ElectraSyn 2.0 is a recently commercialized electrochemistry kit specifically designed to standardize electrolysis apparatus and facilitate the adaptation of electrochemistry in synthetic applications. All components of the system are commercially available (see ‘Materials’). In this report, we demonstrate the use of this setup in a 0.3 mmol scale synthesis of 1-(*t*-butyl)-4-(1,2-diazidoethyl)benzene (**2**) (Box 1).

The alternative commercial setup is a modified adaptation of previously reported systems[28–30] and comprises a three-neck round-bottom flask, commercial electrodes, and other common small laboratory equipment (see ‘Materials’). This system is amenable to reactions of all scales. We demonstrate the use of

Box 2 | Preparation of the electrochemical cell and cell top for section 1 ● Timing 30 min

This box details the preparation of the electrolysis setup used in section 1. The electrochemical cell (a custom-made two-neck glass tube) is prepared by a glassblower using commercially available materials (see below). The schematic is given in this box and Supplementary Fig. 6, whereas the detailed procedure is not provided here.



this setup in a 3 mmol scale (~0.8-g scale) synthesis of **2** and its tandem reduction to 1-(*t*-butyl)-4-(1,2-diaminoethyl)benzene, using a standard Palladium on carbon hydrogenation procedure (section 3).

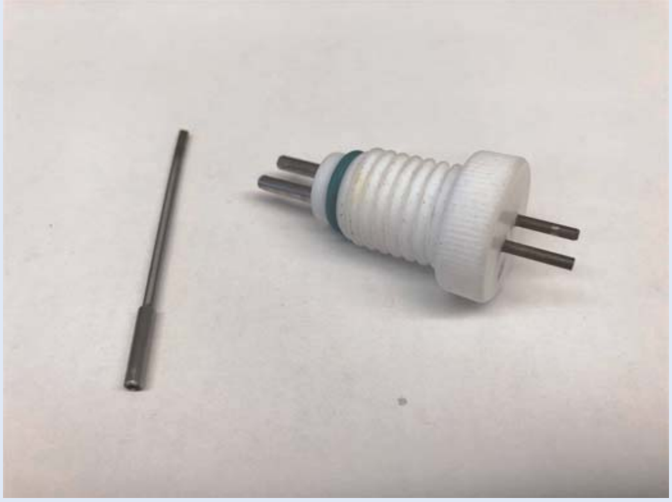
The custom setup was also inspired by previously reported systems[31–33]. Although it requires preparative work to produce the reaction vessel, the system is highly modular and easy to assemble. Our detailed vessel design is included in Box 2, but analogous approaches should also suffice. This setup is preferable for small-scale reactions intended primarily for discovery and optimization. In this report, we demonstrate its use in a 0.2 mmol scale (~50 mg scale) synthesis of **2** (section 1).

Electrolysis method

Using our electrochemical setup, we can carry out two modes of electrolysis: constant current electrolysis and constant cell-potential electrolysis. For small-scale reactions, which are typically used for reaction discovery and optimization, we attempted to use both modes of electrolysis. The constant cell voltage method is more frequently used, as it allows for control of the oxidizing or reducing power, which usually leads to selective redox transformations of the target FG. For scaled-up syntheses, which follow the optimal conditions developed on a smaller scale, we use constant current electrolysis because it allows for precise control of the speed and total amount of charge passing through the cell, thus enabling control of the conversion and rate of the reaction. Although a three-electrode setup involving a reference electrode allows for finer control of the potential applied to the anode, we will not discuss it in this protocol, as it requires a potentiostat.

Box 2 | (continued)

The cell top is made in a machine shop using commercially available materials. A generic procedure for preparing the Teflon cap with electrical feedthroughs is given in this box.



Additional materials

Two-neck glass tube

Internal glass thread (no. 15; Chemglass, cat. no. CG-360-03)
Ground joint (14/20 outer join; Chemglass, cat. no. CG-105-06)

Teflon cell cap

Steel rod (2-mm diameter)
Steel tubing (2-mm inner diameter, 3-mm outer diameter)
Teflon cap (no. 15 Teflon bushing; Chemglass, cat. no. CG-366-12)
Locking pliers
Wire cutter
File
Rubber mallet
Drill press
Drill press vise
Drill bit (1/16 inch)
Level scrap material (e.g., wood)
Silicone/PTFE septum (for 15-425 screw cap; Fisher, cat. no. 03-394A)

Procedure

Preparation of electrical feedthroughs

1. Cut a piece of a 2-mm-diameter steel rod to 5 cm in length with a wire cutter.
2. Cut a piece of 2-mm-internal-diameter steel tubing to 1.5 cm in length with a wire cutter.
3. Using a file, smooth the rough edges of the sections of the steel tubing. We found that gripping the tubing with a pair of locking pliers made this process much easier.
4. Using a file, smooth the edges of the steel rod. File both ends such that the edges are rounded or slanted. This will make it easier to insert the steel rod into the tubing.
5. Grip the steel rod from step 4 firmly with a pair of locking pliers such that 5 mm of the rod extends from the side of the pliers.
6. Using a rubber mallet, drive the 5-mm section of the rod into the steel tubing.
   ? TROUBLESHOOTING
7. Repeat Steps 1–6 to construct the second feedthrough.

Preparation of the Teflon cap

8. Mark the underside of the Teflon cap where the two holes are to be drilled. Evenly space the marks ~6 mm apart from each other.
9. Place a drill press vise under the bit of a drill press. Place a level piece of scrap material on the drill press vise. Tighten the drill press vise on the Teflon cap, making sure that the cap is level.
   ▲CRITICAL STEP The piece of scrap material should be (i) at least 5 mm shorter than the mouth of the drill press vise and (ii) narrower than the Teflon cap. This should allow the upside-down Teflon cap to be clamped in place on the level scrap material (wood) surface.
10. Insert a 1/16-inch drill bit into the drill press and drill through the cap. Advance the drill slowly and retreat occasionally for the cleanest cut.
11. Clear the hole of any residual Teflon shavings.
12. Repeat Steps 9–11 to create the second hole in the Teflon cap.
13. Advance an electrical feedthrough from Step 7 into each hole using a rubber mallet.

Product isolation and tandem reduction

Owing to the good solubility of most reaction components in water, including the Mn catalyst, sodium azide, the electrolyte, and acetic acid, the workup of the reaction can often be simplified when the conversion and product selectivity are high. In most cases, a standard aqueous workup was sufficient to remove the polar components of the reaction mixture and recover predominantly the 1,2-diazide product in the organic phase. This crude product can be directly subjected to the reduction step to form 1,2-diamine, thus reducing any potential hazard caused by the shock sensitivity of the organic azide intermediate.

Many methods have been reported for the reduction of organic azides to their corresponding amines[34–37]. In this protocol, we describe catalytic hydrogenation by palladium on carbon (Pd/C). Other reagents that we tested successfully for the conversion of 1,2-diazides to 1,2-diamines include PPh_3/H_2O via Staudinger reduction[34] and propane-1,3-dithiol[35]. The suitable reduction method should be selected on a per substrate basis.

Materials

Reagents

! CAUTION Appropriate personal protective equipment, including lab coats, gloves, and safety glasses, should be used while performing the protocolToxic, pyrophoric, and explosive chemicals should be handled with care. All chemical reactions and product purification should be performed in a well-ventilated fume hood.

- 1-(*t*-Butyl)-4-vinylbenzene (Sigma-Aldrich, cat. no. 523933)
- Manganese bromide tetrahydrate ($MnBr_2{\cdot}4H_2O$; Sigma-Aldrich, cat. no. 208434)
- Sodium azide (NaN_3; Acros, cat. no. AC190381000) **! CAUTION** Sodium azide is a toxic and shock-sensitive solid, and should be handled with caution.
- Lithium perchlorate ($LiClO_4$; Acros, cat. no. 194711000) **! CAUTION** Lithium perchlorate is a potentially explosive solid and should be handled with caution. $LiClO_4$ can be replaced with tetrabutylammonium hexafluorophosphate with little effect on reaction outcome.
- Acetic acid (HOAc; Macron, cat. no. 8817-46)
- Acetonitrile (MeCN; Fisher, cat. no. A998-4)
- Palladium on carbon (Pd/C; Sigma-Aldrich, cat. no. 205699) **! CAUTION** Pd/C is a pyrophoric solid.
- Celite (Fisher, cat. no. EM-CX0574-3)
- Toluenesulfonic acid monohydrate ($TsOH{\cdot}H_2O$; Millipore Sigma, cat. no. T35920)
- Sodium bicarbonate ($NaHCO_3$; Fisher, cat. no. 5233-3)
- Methanol (MeOH, Fisher, cat. no. A412-4)
- Ethyl acetate (Fisher, cat. no. E14520)
- Hexanes (Fisher, cat. no. H29220)
- Ether (Fisher, cat. no. 6138-20)
- Dichloromethane (Fisher, cat. no. D37-20)
- Hydrogen gas (99.9995%; Airgas)
- Nitrogen gas (industrial-grade liquid nitrogen; Airgas)

Equipment

For section 1

- Direct-current (DC) power supply (HY-ELEC, model no. HY3001MR; any DC power supply with an output voltage range of 0–10 V or larger and an output current range of 0–100 mA or larger, such as HY-ELEC, model nos. HY3005M and HY3005MR, and B&K Precision, model no. 1739, should in principle provide identical performance)
- Electrical leads (Pomona, cat. no. 1166-36-2)
- Two-necked glass tube (custom made, main neck: no. 15 internal thread, side neck: 14/20 joint; see Box 2 and Supplementary Fig. 6)
- Teflon cap with stainless steel feedthrough (custom made from no. 15 Teflon bushing; Chemglass, cat. no. CG-366-12; see Box 2 and Supplementary Figs. 7–9)
- Platinum wire (0.3-mm diameter; Alfa Aesar, cat. no. AA43014BU)
- Magnetic hotplate stirrer (Corning, model no. PC-420D)
- Reticulated vitreous carbon (100 pores per inch, surface area ~65 cm^2/cm^3; ERG Aerospace)
- Graphite rod (2B pencil lead, 2-mm diameter, ~9 cm long)

- Electrical multimeter (HY-ELEC, model no. MS8236)
- Teflon tape (Black Swan, part no. 02090-10)

For section 2

- Direct-current (DC) power supply (HY-ELEC, model no. HY3001MR; any DC power supply with an output voltage range of 0–10 V or larger and an output current range of 0–100 mA or larger, such as HY-ELEC, model nos. HY3005M and HY3005MR, and B&K Precision, model no. 1739, should in principle provide identical performance)
- Electrical leads (Pomona, cat. no. 1166-36-2)
- Three-necked round-bottom flask (50 mL, 14/20 joint)
- Rubber septa (14/20; VWR, cat. no. 89097-554)
- Magnetic hotplate stirrer (Corning, model no. PC-420D)
- Reticulated vitreous carbon (100 pores per inch, surface area ca. 65 cm^2/cm^3; ERG Aerospace)
- Graphite rod (2B pencil lead, 2-mm diameter, ~9 cm long)
- Platinum wire (0.3-mm diameter; Alfa Aesar, cat. no. AA43014BU)
- Platinum foil (2.5 × 1.5 × 0.025 cm; Alfa Aesar, cat. no. AA11508FF)
- Electrical multimeter (HY-ELEC, model no. MS8236)

For section 3

- Gas inlet adapter bearing a glass stopcock (14/20 joint, Kemtech America, cat. no. A751420)
- Three-necked round-bottom flask (25 mL, 14/20 joint)

For all sections

- Balloons
- Stir bar
- Syringes (1, 3, 6, and 12 mL)
- Hypodermic needles (18, 20, and 22 gauge, 1.5 inch and 22 gauge, 3 inch)
- Glass vials (1.5 dram and 20 mL)
- Rotary evaporator
- NMR spectrometer
- Schlenk line (Chemglass, cat. no. AF-0452)

Procedure

▲**CRITICAL** Section 1 (Steps 1–28) describes the small-scale (0.2 mmol) synthesis of 1,2-diazide 2 using a custom-made electrochemical setup. Section 2 (Steps 29–47) describes the large-scale (3 mmol) synthesis of 2 using an electrochemical cell derived from commercial equipment. Section 3 (Steps 48–64) details the reduction of 2 to the corresponding 1,2-diamine using hydrogenation catalyzed by Pd/C.

Section 1—Electrosynthesis of 1,2-diazides (0.2 mmol scale):

Part 1—preparation of the carbon anode ● Timing 2 min

1 Wash a piece of pencil lead (2B pencil lead, 7 cm in length, 2 mm in diameter; Fig. 3a) with acetone and dry it in air.

2 Insert one end of the pencil lead into a piece of RVC cut to 1 × 0.5 × 0.6 cm (Fig. 3b). The entire RVC (~20 cm^2 surface area) will be submerged in solution.

Part 2—preparation of the platinum cathode ● Timing 5 min

3 Cut a 12- to 13-cm-long, 0.3-mm-diameter piece of Pt wire, which will correspond to a surface area of ~100 mm^2 exposed in solution.

4 Wrap one end of the Pt wire (1.4–2.4 cm long) around a piece of pencil lead tightly. The length of Pt wire exposed to solution should be ~10.6 cm in length.

5 Coil the other end of the Pt wire around another piece of pencil lead and compress the coil to ~1 cm in length. Remove the second pencil lead (Fig. 3c).

6 Use Teflon tape to cover the segment in which the carbon and platinum are in contact. Adjust the length of the pencil lead by cutting it from the bare end such that its length is identical to that of the carbon anode (Fig. 3d).

Part 3—assembly of the electrochemical cell ● Timing 2 min

7 Insert the RVC and Pt electrodes into the conductive sockets (2-mm inside diameter) of the custom-made Teflon cap fitted with brass electrical feedthroughs. The two lower ends of the electrodes should be ~2–3 mm apart (Fig. 3e,f).

▲CRITICAL STEP The Teflon cap is custom made from a standard no. 15 Teflon bushing (see Box 2 and Supplementary Figs. 7–9). The cap must be airtight when fitted onto the glass tube. Introduction of oxygen into the reaction system may lead to side products from O_2 trapping of radical intermediates.

8 Test the electrical connection between each electrode and the cap with a multimeter. The resistance of the RVC electrode (from the end of the RVC electrode to the external end of the brass feedthrough) should be <30 Ω, whereas the resistance of the Pt electrode (from the end of the Pt wire to the external end of the brass feedthrough) should be <10 Ω.

? TROUBLESHOOTING

Part 4—electrolysis ● Timing 2.5 h

9 Charge a 10-mL two-neck glass tube (custom made) with a Teflon-coated magnetic stir bar, the catalyst ($MnBr_2 \cdot 4H_2O$, 2.8–2.9 mg, 0.010 mmol, 5 mol%) and NaN_3 (65.0 mg, 1.0 mmol, 5.0 equiv.).

10 Seal the main neck of the glass tube with the Teflon cap from Step 7.

11 Seal the side neck (14/20 joint) with a rubber septum (Fig. 3g).

12 Pierce the rubber septum with a long needle connected to a nitrogen inlet line. The tip of the needle should be maintained close to the bottom of the tube. Pierce the rubber septum again with an additional needle to serve as a gas outlet.

13 Flush the tube with nitrogen gas for ~5 min.

14 Using a syringe, add the electrolyte solution (3.0 mL, 0.1 mol/L $LiClO_4$ in CH_3CN) through the septum on the side neck.

▲CRITICAL STEP Tetrabutylammonium hexafluorophosphate (0.1 mol/L in CH_3CN) was also tested and proved effective as an electrolyte in the diazidation protocol.

15 Purge the mixture with nitrogen gas for ~5 min. Stirring is not necessary during this step.

16 Weigh 1-(t-butyl)-4-vinylbenzene (32.0 mg, 0.2 mmol, 1.0 equiv.) into a vial and dissolve it with electrolyte solution (0.5 mL, 0.1 mol/L $LiClO_4$ in CH_3CN) and glacial acetic acid (HOAc, 0.4 mL).

17 Add this solution to the tube using a syringe and then purge the whole reaction mixture with nitrogen gas for another 1 min. Stirring is not necessary during this step.

▲CRITICAL STEP Remaining oxygen in the reaction system may lead to side products.

18 Remove both the inlet and outlet needles.

19 Measure the resistance between the two brass feedthroughs outside the electrolysis cell. The resistance should be no larger than 35 KΩ.

? TROUBLESHOOTING

20 Pierce the rubber septum with a needle connected to a nitrogen-filled balloon to sustain a nitrogen atmosphere.

21 Connect the electrodes to a DC power supply with the positive lead connected to the feedthrough housing the RVC electrode and the negative lead connected to the feedthrough housing the Pt electrode. Apply potential (2.3 V) to electrolyze the solution for 2 h at room temperature (Fig. 3h). The steady-state current is typically 5–8 mA (current density ~0.25–0.4 mA/cm^2 based on the actual surface area of the RVC electrode).

▲CRITICAL STEP The reaction can be monitored using thin-layer chromatography (TLC). A sample can be obtained via a capillary under positive N_2 pressure. In hexanes/ethyl acetate (20:1), the R_f values of alkene 1 and 1,2-diazide 2 are 0.72 and 0.24, respectively. When scaled up, the reaction can take a longer time to reach completion. 1,2-Diazides, if not directly visible on a TLC plate under UV irradiation, can be visualized by exposure to UV light (254 nm) for ~30 s, upon which the 1,2-diazide spot on the TLC plate will become UV-active, presumably from photoinduced degradation. If the reaction is incomplete with remaining alkene 1 observed, extending the electrolysis time is recommended.

? TROUBLESHOOTING

22 After disconnecting the reaction from the DC power supply, gently remove the Teflon cap with electrodes from the tube and transfer the reaction mixture to a separatory funnel. Wash the electrodes with ethyl acetate (10 mL) to transfer residual product to the separatory funnel.

23 Add an additional 20 mL of ethyl acetate to the separatory funnel and wash the organic layer with saturated aqueous $NaHCO_3$ (20 mL × 3).
24 Dry the organic layer with anhydrous sodium sulfate (~5.0 g) and decant it into a round-bottom flask.
25 Remove the solvent using a rotary evaporator.
26 Obtain an NMR reading of the residue. The product should appear spectroscopically pure.
? TROUBLESHOOTING
27 If the product is impure, purify it using flash column chromatography (silica gel, 1.5-cm i.d. × 20-cm length) with hexanes/ethyl acetate as eluent (gradient from 20:1 to 10:1). Collect the fractions containing the product and evaporate the solvent to dryness under vacuum at a temperature no higher than 45 °C to afford 2 as a pale-yellow oil.
■ **PAUSE POINT** The product is stable and can be stored at 4 °C for at least 6 months without degradation as judged by ^1H NMR.

Part 5—cleaning of the electrodes ● Timing 6 min

28 Clean the Pt electrode by submerging it in concentrated nitric acid (~70%) for 5 min, followed by rinsing it with water and then acetone. Dispose of the graphite rod and RVC after use.
▲ **CRITICAL STEP** Not cleaning Pt electrode properly may lead to irreproducible results.

Section 2—Electrosynthesis of 1,2-diazides (3 mmol scale):

Part 1—preparation of the carbon anode ● Timing 2 min

29 Insert a graphite rod (9 cm in length, 2 mm in diameter) into a piece of RVC cut to cylinder shape (1.0 cm in diameter and 1.5 cm in length; surface area ~76.5 cm^3). The entire piece of RVC will be submerged in solution (Fig. 4a).

Part 2—preparation of the platinum cathode ● Timing 5 min

30 Thread a platinum wire (22 cm) through a piece of platinum foil (2.5 × 1.5 × 0.025 cm) through holes (punched using an 18-gauge needle) close to one end of the foil (Fig. 4a).

Part 3—assembly of the electrochemical cell ● Timing 5 min

31 Fit the RVC and Pt electrodes through two separate 14/20 rubber septa (Fig. 4b). We recommend using an 18-gauge needle to assist in creating holes of appropriate sizes for feeding the electrodes through the septa. The fitting needs to be airtight.
32 Fit the septum with the RVC anode onto the central neck of a 50 mL three-neck round-bottom flask and fit the one with the Pt cathode onto one side neck. Adjust the electrodes so the lower ends of the two electrodes are ~5 mm apart. Bend and fix the part of the Pt wire outside the flask to the side neck using electrical tape. Fit the other side neck with a new, unused rubber septum.
▲ **CRITICAL STEP** Although not necessary, taping the Pt wire to the side neck helps to immobilize the Pt foil immersed in the reaction mixture. During the reaction, if the Pt foil comes into contact with the RVC, the system will be shorted, and no current will pass through the reaction medium.

Part 4—electrolysis ● Timing 4.5 h

33 Charge the three-neck round-bottom flask from Step 32 with a Teflon-coated magnetic stir bar, $MnBr_2 \cdot 4H_2O$ (43 mg, 0.15 mmol, 5 mol%), and NaN_3 (975 mg, 15 mmol, 5.0 equiv.).
34 Pierce the new rubber septum with a long needle connected to a nitrogen inlet line, maintaining the tip of the needle close to the bottom of the flask. Pierce this rubber septum again with an additional needle to serve as a nitrogen outlet.
35 Flush the flask with nitrogen gas for ~5 min.
36 Using a syringe, add a mixture of electrolyte solution (24 mL, 0.1 mol/L $LiClO_4$ in CH_3CN), 1-(*t*-butyl)-4-vinylbenzene (480 mg, 3.0 mmol, 1.0 equiv.), and acetic acid (6.0 mL) to the flask.
37 Purge the mixture with nitrogen gas for ~5 min. Stirring is not necessary during this step.
▲ **CRITICAL STEP** Remaining oxygen in the reaction system may lead to side products.
38 Remove the inlet and outlet needles.
39 Pierce the rubber septum bearing no electrode with a needle connected to a nitrogen-filled balloon to sustain a nitrogen atmosphere.
40 Connect the electrodes to a DC power supply, with the carbon electrode attached to the positive lead and the Pt electrode attached to the negative lead. Electrolyze the mixture at a constant current of

40 mA (current density ~0.5 mA/cm^2 based on actual surface area of the RVC electrode) for 4 h at room temperature (Fig. 4c).

▲**CRITICAL STEP** Monitoring the reaction progress by TLC every 1–2 h is highly recommended. A sample (<5 μL) can be obtained via a capillary under positive N_2 pressure. If the reaction is incomplete (remaining alkene 1 is observed), extending the electrolysis time is recommended.

? TROUBLESHOOTING

41 After disconnecting the reaction from the DC power supply, remove the septa from the flask and transfer the reaction mixture to a separatory funnel. Wash the electrodes with ethyl acetate (10 mL) to transfer residual product to the separatory funnel.

42 Add 40 mL of ethyl acetate to the separatory funnel and wash the organic layer with saturated aqueous $NaHCO_3$ (30 mL × 3).

43 Dry the organic layer with anhydrous sodium sulfate (~10 g) and decant it into a round-bottom flask.

44 Using a rotary evaporator, remove the solvent to dryness under vacuum at a temperature no higher than 45 °C.

45 Obtain an NMR reading of the residue. The product should appear spectroscopically pure.

? TROUBLESHOOTING

46 If the crude product is impure, purify it using flash column chromatography (silica gel, 4.0 -m i.d. × 15-cm length) with hexanes/ethyl acetate as the eluent (gradient from 20:1 to 10:1) to afford 2 as a pale-yellow oil.

■**PAUSE POINT** The product is stable and can be stored at 4 °C for at least 6 months without degradation as judged by ^1H NMR.

Part 5—cleaning of the Pt electrode ● Timing 3 min

47 Run the Pt plate through the flame of a butane torch until it glows orange. Allow it to cool for 1 min before any future use. Alternatively, the electrode can be cleaned by following Step 28 of section 1. Dispose of the graphite rod and RVC after use.

▲**CRITICAL STEP** Failure to clean the Pt electrode properly may lead to irreproducible results.

Section 3—Reduction of 1,2-diazide 2 to the corresponding 1,2-diamine ● Timing 13 h

48 Add 10.0 mL of methanol to the crude 1,2-diazide **2** (from Step 44, 244 mg, 1.0 mmol) in order to dissolve it.

49 Equip a 25-mL three-neck-round bottom flask with a greased gas inlet adapter bearing a glass stopcock and two rubber septa. Attach the flask to a Schlenk line using the adapter.

50 Charge the flask with a Teflon-coated magnetic stir bar and Pd/C (20.0 mg, 10 wt%).

51 Using the Schlenk line, evacuate and gently backfill the flask with N_2 three times.

52 Inject the solution of **2** from Step 48 into the flask via a syringe.

53 Prepare an H_2-filled balloon connected to a needle.

54 Evacuate the flask using the Schlenk line and refill it with H_2 using the H_2-filled balloon. Repeat this process one more time. Seal the flask by closing the glass stopcock of the gas inlet adapter and disconnect it from the Schlenk line.

55 Pierce one of the rubber septa with a needle connected to a H_2-filled balloon to sustain a hydrogen atmosphere throughout the reaction.

56 Stir the mixture solution vigorously and monitor the reaction progress via TLC. Samples (<5 μL) are removed via a capillary under a positive H_2 atmosphere about every 2–4 h. The reaction is typically finished in 12 h.

57 Remove Pd/C by filtration through Celite and wash the filter cake with additional methanol (10 mL × 3).

58 Using a rotary evaporator, concentrate the combined filtrate solution to dryness at 40 °C.

59 Dissolve the residue in 10.0 mL of ether.

60 Add this crude product solution to a solution of $TsOH{\cdot}H_2O$ (2.0 mmol in 10.0 mL of ether) and stir the resultant mixture for 10 min.

61 Collect the white precipitate by filtration.

62 Dissolve the white solid in saturated aqueous $NaHCO_3$ (30 mL) and extract the aqueous layer with dichloromethane (3 × 20 mL).

63 Dry the combined organic layers with anhydrous sodium sulfate (~5.0 g) and decant it into a round-bottom flask.

64 Using a rotary evaporator, remove the solvent to dryness at 40 °C to afford 1-(*t*-butyl)-4-(1,2-diaminoethyl)benzene.

Troubleshooting

Troubleshooting advice can be found in Table 2.

Table 2 | Troubleshooting table

Step	Problem	Possible reason	Solution
8	Resistance is too high	Faulty connection between two conducting materials	Sand the ends of the electrode to be inserted into the cap with a fine-grit sandpaper. The sockets in the Teflon cap can also be cleaned with 1 M aqueous hydrochloric acid, followed by rinsing with water and acetone
12	Cell voltage too high	(i) Connection issue or (ii) electrodes are too far apart	(i) See advice for Step 8 or (ii) reduce the distance between the two electrodes
17, 26	NMR indicates remaining starting material	(i) Inadequate electrolysis time or (ii) unproductive NaN_3 consumption	(i) Extend electrolysis or (ii) add more NaN_3
19	Resistance is too high	Faulty connection between different points	Remove the Teflon cap, test each electrical connection point, and reassemble
21	No/low current	(i) Connection issue or (ii) electrodes are too far apart	(i) See advice for Step 8 or (ii) reduce the distance between the two electrodes
Box 1, step 27	Low yielding	(i) Incomplete reaction or (ii) by-product formation	(i) Extend the reaction time or (ii) lower the electrolysis potential from 2.3 to 2.1–2.2 V
Box 2, step 6	The steel rod does not fit into the steel tubing	The steel rod is too thick	File the surface of the 5-mm section of the rod until modest percussive force joins the rod and tubing

Timing

Section 1—Steps 1–8, preparation of the reaction setup: 9 min
Section 1—Steps 9–27, electrolysis: 2.5 h
Section 1—Step 28, cleaning of the electrodes: 6 min
Section 2—Steps 29–32, preparation of the reaction setup: 12 min
Section 2—Steps 33–46, electrolysis: 4.5 h
Section 2—Step 47, cleaning of the Pt electrode: 3 min
Section 3—Steps 48–64, reduction of 1,2-diazide **2** to the corresponding 1,2-diamine: 13 h
Box 1, diazidation with ElectraSyn 2.0: 2.5 h
Box 2, preparation of the electrochemical cell and cell top for section 1: 30 min

Anticipated results

Analytical data

1-(t-Butyl)-4-(1,2-diazidoethyl)benzene (2)

Yield = 90–96% (range of yields over more than five experiments).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, J = 8.3 Hz, 2 H), 7.24 (d, J = 8.2 Hz, 2 H), 4.64. (dd, J = 8.4, 4.8 Hz, 1 H), 3.52–3.39 (m, 2 H), 1.31 (s, 9 H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 152.07, 133.24, 126.58, 125.96, 65.30, 55.92, 34.64, 31.22.
IR (film) 2,964, 2,869, 2,096, 1,510, 1,462, 1,440, 1,397, 1,312, 1,268, 1,109, 1,015, 831, 658 cm^{-1}.
High-resolution mass spectrometry (HRMS; direct analysis in real time (DART) ion source) for $[(C_{12}H_{17}N_6)^+ - N_2]$: calculated 217.1448, found 217.1447.
TGA: see Fig. 5.

1-(t-Butyl)-4-(1,2-diaminoethyl)benzene

Yield = 84%.
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (d, J = 8.1 Hz, 2 H), 7.32–7.23 (m, 2 H), 3.91 (t, J = 6.1 Hz, 1 H), 2.93 (dd, J = 12.4, 5.1 Hz, 1 H), 2.84 (dd, J = 12.4, 7.1 Hz, 1 H), 1.53 (s, 4 H), 1.34 (s, 9 H).
^{13}C NMR (125 MHz, $CDCl_3$) δ 150.07, 141.23, 126.14, 125.39, 58.00, 49.93, 34.44, 31.34.
IR (film) 3,288, 2,960, 2,866, 1,578, 1,509, 1,263, 1,141, 829 cm^{-1}.
HRMS (DART) for $[(C_{12}H_{21}N_2)^+]$: calculated 193.1699, found 193.1704.
TGA: see Fig. 6.

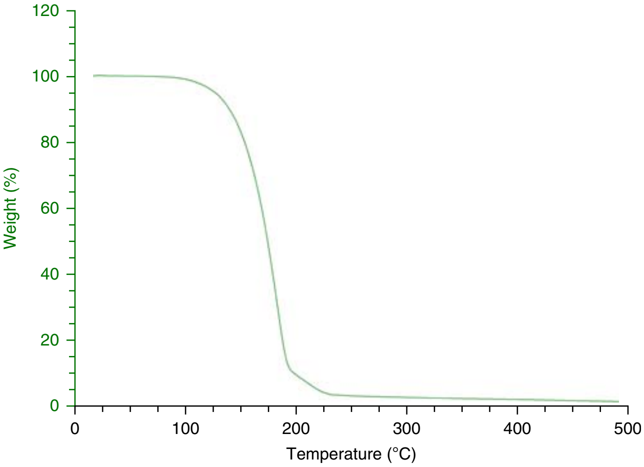


Fig. 5 | TGA data for 1,2-diazide 2.

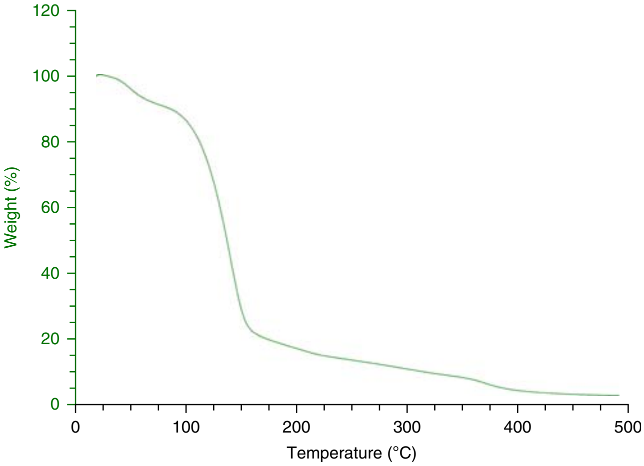


Fig. 6 | TGA data for 1-(*t*-butyl)-4-(1,2-diaminoethyl)benzene (product from reduction of 2).

Additional TGA data for compounds **3**, **4**, **7**, **9**, **13**, and NaN_3 are provided in Supplementary Figs. 10–15.

(2,3-Diazidopropyl)benzene (16)
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38–7.35 (m, 2 H), 7.33–7.29 (m, 1 H), 7.26–7.20 (m, 2 H), 3.77–3.71 (m, 1 H), 3.43 (dd, $J = 12.7$, 4.0 Hz, 1 H), 3.32 (dd, $J = 12.7$, 6.9 Hz, 1 H), 2.91 (d, $J = 7.1$ Hz, 2 H).
^{13}C NMR (125 MHz, $CDCl_3$) δ 136.29, 129.24, 128.79, 127.16, 62.87, 53.87, 37.99.
(1,2,3-Triazidopropyl)benzene (17). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51–7.39 (m, 5 H), 4.65 (dd, J = 7.9, 2.5 Hz, 1 H), 3.56–3.47 (m, 2 H), 3.17–3.08 (m, 1 H).
^{13}C NMR (125 MHz, $CDCl_3$) δ 135.06, 129.44, 129.22, 127.81, 66.03, 65.09, 51.75.
For the ^{1}H and ^{13}C NMR spectra of a mixture of **16** and **17**, see Supplementary Figs. 16 and 17.

Application of section 1 in the synthesis of products 3–15

General guidelines

Alkenes less reactive than **1** (e.g., monosubstituted aliphatic alkenes and electron-deficient alkenes) usually require stronger forcing conditions to obtain synthetically useful yields. In most cases surveyed in this article, increasing the reaction temperature to 40 °C or the catalyst loading to 10 mol%, or both, can resolve the reactivity issue. Examples are given below for the synthesis of products **3**, **7**, **8**, **10**, **12**, **14**, and **15**.

For **3** and **7**: in section 1, between Steps 20 and 21, instead of running the electrolysis at room temperature, warm the reaction to 40 °C using an oil bath before connecting the DC power supply. Maintain a temperature of 40 °C throughout the electrolysis.

For **8**, **10**, **12**, and **14**: in section 1, Step 9, instead of adding 2.8 mg of $MnBr_2$, add 5.7 mg.

For **15**: in section 1, Step 16, instead of adding 0.4 mL of HOAc, add 0.3 mL; between steps 20 and 21, instead of running the electrolysis at room temperature, warm the reaction to 40 °C using an oil bath before connecting the DC power supply. Maintain a temperature of 40 °C throughout the electrolysis.

Further information on experimental design is available in the **Life Sciences Reporting Summary**.

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Author contributions

N.F. and S.L. designed the experiments. N.F. and G.S.S. carried out the experiments. N.F., G.S.S., and S.L. wrote the manuscript.

Competing interests

The authors declare no competing interests.

Additional information

Supplementary information is available for this paper at https://doi.org/10.1038/s41596-018-0010-0.

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[redacted]

Related Links

Key references using this protocol

1. Fu, N., Sauer, G.S., Saha, A., Loo, A. & Lin, S. *Science*, **357**, 575–579 (2017). https://doi.org/10.1126/science.aan6206
2. Fu, N., Sauer, G.S. & Lin, S. *J. Am. Chem. Soc.* **139**, 15548–15553 (2017). https://doi.org/10.1021/jacs.7b09388
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Experimental design

1. Sample size

Describe how sample size was determined.	Over 40 alkene substrates were tested using the reported protocol, and 15 representative examples are presented in figure 2. The substrates were chosen so the sensitivity of the reaction protocol to alkene substitution patterns and functional groups could be investigated.

2. Data exclusions

Describe any data exclusions.	No data were excluded.

3. Replication

Describe whether the experimental findings were reliably reproduced.	The experiments were reliably reproduced by all non-corresponding authors and one other person in our laboratory.

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Describe whether the investigators were blinded to group allocation during data collection and/or analysis.	This is not relevant to our reaction protocol development.

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9. Antibodies

Describe the antibodies used and how they were validated for use in the system under study (i.e. assay and species).	No antibodies were used.

10. Eukaryotic cell lines

a. State the source of each eukaryotic cell line used.	No eukaryotic cell line was used.
b. Describe the method of cell line authentication used.	No eukaryotic cell line was used.
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Describe the covariate-relevant population characteristics of the human research participants.	No human participants were involved.