

Quinone-mediated hydrogen anode for non-aqueous reductive electrosynthesis

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Electrochemical synthesis can provide more sustainable routes to industrial chemicals¹⁻³. Electrosynthetic oxidations often may be performed "reagent-free", generating H₂ derived from the substrate as the sole byproduct at the counter electrode. Electrosynthetic reductions, however, require an external source of electrons. Sacrificial metal anodes are commonly used for small-scale applications⁴, but more sustainable options are needed at large scale. Anodic water oxidation is an especially appealing option^{15,6}, but many reductions require anhydrous, air-free reaction conditions. This constraint motivates the growing interest in the electrochemical hydrogen oxidation reaction (HOR) under non-aqueous conditions⁷⁻¹². Here, we report a mediated H₂ anode that achieves indirect electrochemical oxidation of H₂ by pairing thermal catalytic hydrogenation of an anthraquinone mediator with electrochemical oxidation of the anthrahydroquinone. This quinone-mediated H₂ anode is used to support nickel-catalyzed cross-electrophile coupling (XEC), a reaction class gaining widespread adoption within the pharmaceutical industry¹³⁻¹⁵. Initial validation of this method in small-scale batch reactions is followed by adaptation to a recirculating flow reactor that enables hectogram-scale synthesis of a pharmaceutical intermediate. The

mediated H₂ anode technology disclosed here offers a general strategy to support H₂-driven electrosynthetic reductions.

Electrochemical HOR is well established in fuel cells (Fig. 1a). Humidified H₂ gas is delivered to the anode within a membrane-electrode assembly (MEA) that incorporates gas-diffusion, catalyst, and proton-exchange-membrane (PEM) layers. This approach is not readily adapted to organic electrosynthesis in non-aqueous media because protons derived from HOR migrate to the cathode through the PEM layer accompanied by significant quantities of water. For typical electrosynthetic reductions, water would accumulate in concentrations of 1–5 M in the cathode compartment¹⁶, significantly changing the reaction medium and complicating moisture-sensitive reduction reactions. Gas-diffusion electrodes (GDEs) offer an alternative approach to achieve non-aqueous electrochemical HOR, and they have been used recently to support lithium-mediated N₂ reduction^{9,11}. Contemporary efforts are directed toward mechanistic studies and catalyst design efforts to address the kinetic limitations of electrocatalytic HOR in organic solvent^{7,8,11}. The present study was initiated to explore another strategy, whereby thermal catalytic hydrogenation of a redox-active molecule is used to support indirect electrochemical HOR. Quinone hydrogenation is well established in organic solvent and is featured in the industrial anthraquinone process for hydrogen peroxide synthesis¹⁷. Separately, good electrochemical properties of quinones are evident from their recent use in organic redox flow batteries^{18,19} and mediated fuel cells²⁰. The reversible chemical/electrochemical interconversion of quinone and hydroquinone (**Fig. 1b**) provides the basis for a quinone-mediated H₂ anode to support electrosynthetic reduction reactions. Ni-catalyzed XEC reactions were selected as the cathode reaction for this study (**Fig. 1c,d**). The widespread use of stoichiometric metal reductants (Zn, Mn) in these reactions complicates large-scale applications, due to the non-uniform reactivity and particle properties of these metals, difficulty in suspending dense metal powders in batch reactors, and formation of stoichiometric Zn or Mn salts as waste²¹. These issues have motivated considerable efforts to

develop electrochemical variants of these reactions^{22–31}, and H₂ offers the most atom-economical and sustainable source of electrons for these reactions.

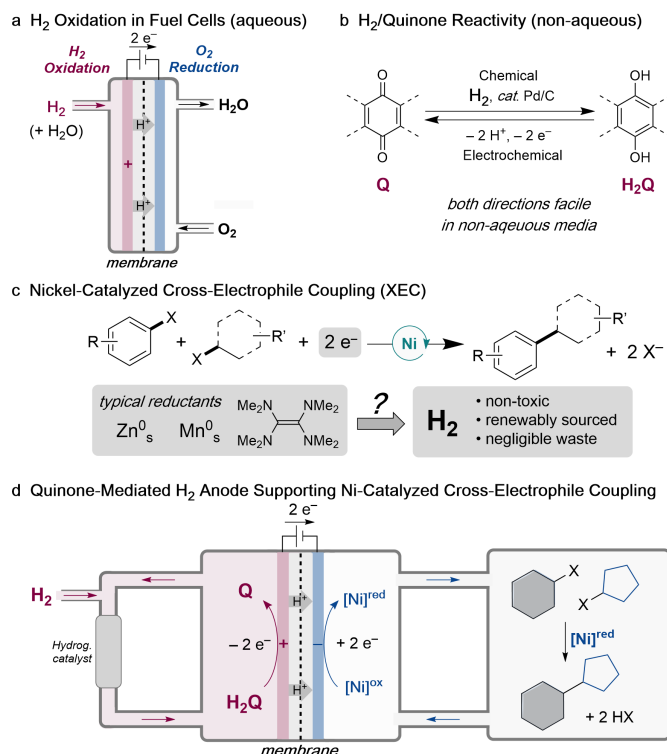


Fig. 1. Strategy to enable the use of H₂ as a source of electrons for Ni-catalyzed cross-electrophile coupling (XEC) in organic solvent. (a) The electrochemical H₂ oxidation reaction (HOR) is a key feature of fuel cells. The essential role of water in supporting HOR and transport of water through the membrane limits use of this method in non-aqueous electrochemistry. **(b)** Catalytic hydrogenation quinones and electrochemical oxidation of hydroquinones are facile in organic solvents. **(c)** Ni-catalyzed cross-electrophile coupling (XEC) is an important and growing class of reduction reactions that would benefit from the ability to use H₂ as a reductant. **(d)** Quinone-mediated H₂ anode concept, designed to support electrochemical Ni-catalyzed XEC.

Ni-catalyzed coupling of aryl and alkyl halides to form C(sp²)–C(sp³) bonds is among the most thoroughly developed class of XEC reactions (see **Fig. 1c**)³². For the present study, we selected a Ni catalyst composed of NiBr₂ and a dual dtbbpy/ttbtpy ligand system, adapted from recent reports^{26,29} (dtbbpy = 4,4'-di-*tert*-butyl-2,2'-bipyridine, ttbtpy = 4,4',4''-tri-*tert*-butyl-2,2':6',2''-terpyridine). Selection of components for the mediated H₂ anode was inspired by recent reports using anthraquinones and other substituted quinones under aqueous conditions for redox flow

batteries^{18,19} and mediated fuel cells^{33,34}. Sodium anthraquinone-2-sulfonate (AQS) exhibits good solubility in polar organic solvents, such as *N,N*-dimethylformamide (DMF) and *N*-methyl-2-pyrrolidone (NMP). Cyclic voltammetry (CV) analysis of AQS in NMP revealed a redox potential of -0.59 V versus a ferrocenium/ferrocene (Fc^+/Fc) reference potential (**Fig. 2a** and **Fig. S3**). This value is 200 mV higher than the H^+/H_2 potential (-0.79 V), measured under the same conditions using CV and open-circuit-potential methods (**Fig. 2a** and **Fig. S2**). CV analysis was also used to probe the redox potentials of nickel bromide complexes bearing the dtbbpy and ttbtpy ligands. The measured two- and one-electron reduction potentials of these complexes range from -1.3 to -2.1 V vs Fc^+/Fc (**Fig. 2a** and **Fig. S4**). The 0.5 – 1.3 V difference between the redox potentials of H_2 and catalytically relevant Ni complexes confirms that H_2 lacks the driving force necessary to serve as a chemical reductant for thermal Ni-catalyzed XEC. Application of an external voltage, however, allows the potential of electrons from H_2 to be raised to the potential needed to support the reactions under electrochemical conditions.

The relative redox potentials of H_2 and AQS indicate that AQS hydrogenation is thermodynamically favorable, and experimental tests further show that this reaction is kinetically facile when using a heterogeneous Pd/C catalyst with 1 atm of H_2 at room temperature (**Fig. S6**). These results provided a starting point for H-cell batch electrolysis experiments to test a mediated H_2 anode system in combination with cathodic Ni-catalyzed XEC (**Fig. 2b**). Both half-cells feature indirect electrochemical processes with a combination of electrochemical and off-electrode chemical reactions (**Fig. 2b**, gray and colored boxes, respectively). Optimization of the H_2 -coupled Ni-catalyzed XEC reaction conditions employed ethyl 4-bromobenzoate and (3-bromopropyl)benzene as the aryl and alkyl electrophiles (**Fig. 2c**). Individual reaction parameters were varied (see section 5 of the Supplementary Information for details) to identify the most effective conditions for this substrate. The following conditions led to formation of the desired $\text{C}(\text{sp}^2)\text{--C}(\text{sp}^3)$ XEC product in 82% yield: 0.2 M aryl bromide as the limiting reagent, 1.25 equiv

of the alkyl bromide, a 10 mol% catalyst composed of $\text{NiBr}_2 \cdot 3\text{H}_2\text{O}$ with a 4:1 ratio of dtbbpy/tbtpy ligands, and 0.2 M LiBr as the supporting electrolyte in NMP. The anode chamber contained

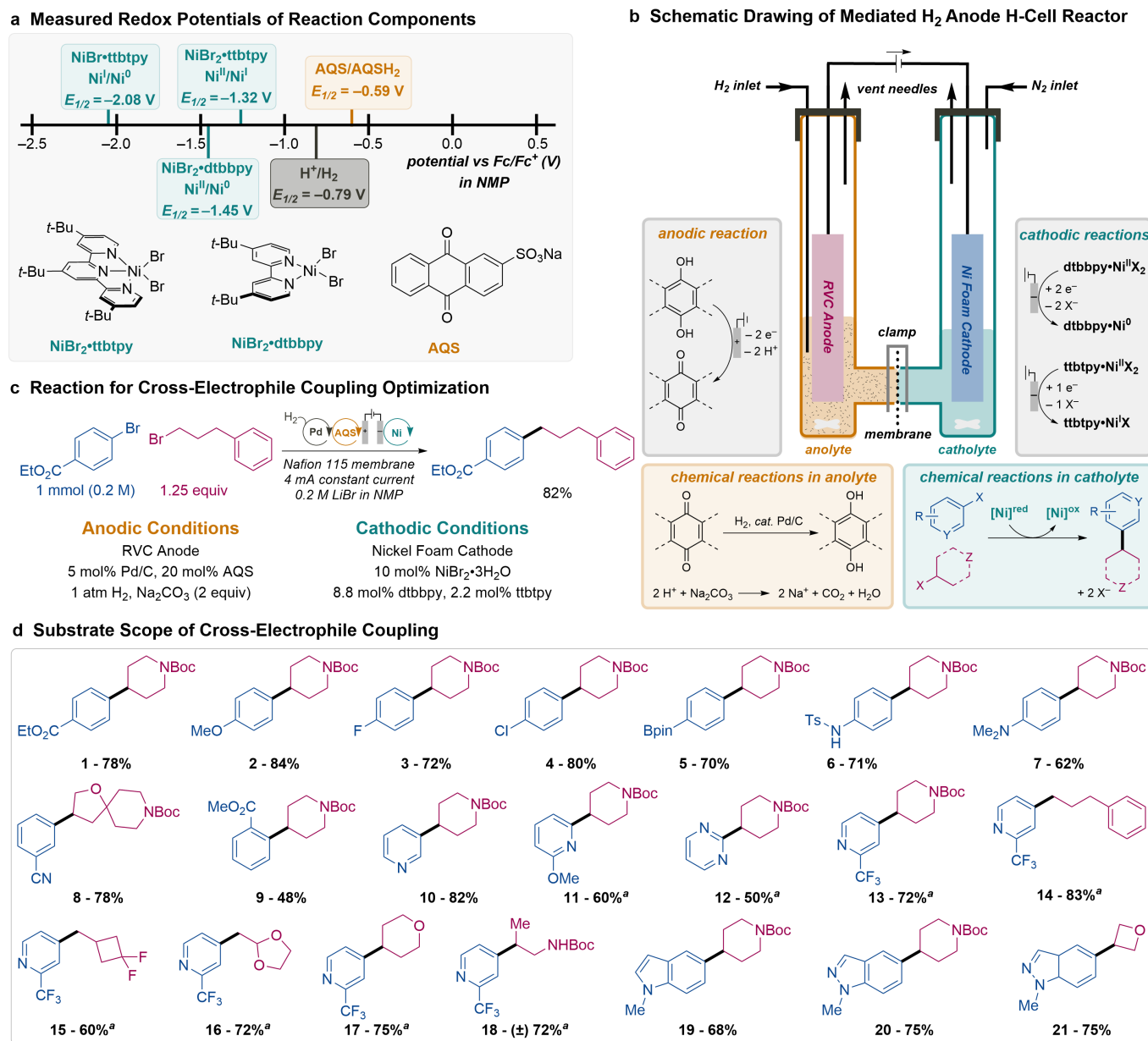


Fig. 2. Voltammetric analysis and electrochemical Ni XEC using a mediated H_2 anode in an H-cell. (a) Redox potentials measured for H_2 , the anthraquinone mediator, and Ni catalyst species show that the potential of H_2 is insufficient to drive Ni XEC in the absence of an electrochemical bias. (b) H-cell schematic illustrating the electrochemical and chemical processes in the anolyte and catholyte compartments. (c) XEC substrates used for reaction testing and optimized reaction conditions. (d) Ni XEC products obtained using the H-cell with a mediated H_2 anode, shown in b, under conditions identical or similar to those in c (see section 10 of the Supplementary Information for details). ^aHeteroaryl chloride used instead of the bromide.

5 wt% Pd/C (with a Pd loading of 5 mol% relative to the Ar–Br), 20 mol% AQS, 2 equiv Na₂CO₃, and 0.2 M LiBr in NMP. These or closely related conditions proved to be effective with a broad range of pharmaceutically relevant coupling partners (**Fig. 2d**). For example, both electron-rich and electron-poor aryl bromides undergo coupling in high yields (**1–4** and **9**), and the method proceeds well with a pendant arylboronic ester group (**5**), a standard reactive group in cross-coupling reactions. This Ni/dtbbpy/tbtpy catalyst system tolerates a range of Lewis basic nitrogen heterocycles, which are prevalent in drug candidates. Examples include pyridines substituted at the 2-, 3-, and 4-position (**10, 11, 13–18**), pyrimidine (**12**), indole (**19**), and indazole (**20, 21**). This catalyst system is also effective with different primary and secondary alkyl bromides (**14–18, 21**), including those with strained rings (**15, 21**) and *tert*-butoxycarbonyl (Boc)-protected primary and secondary amines (**1–13, 19, 20**). These results show excellent compatibility between the mediated H₂ anode and Ni-catalyzed XEC reactions, and they often exceed those obtained in previous studies using the same catalyst system with a tertiary amine reductant^{26,29}.

The primary merits of the mediated H₂ anode will be experienced at larger scale. Therefore, subsequent efforts focused on development of a flow cell that could be integrated with a parallel-plate electrochemical reactor. To facilitate development and testing of the system, the mediated anode was paired with a simple cathodic electron-transfer reaction, involving reduction of Bobbitt's salt, or **ACT**⁺, an oxoammonium compound derived from 4-acetamido-2,2,6,6-tetramethylpiperidine-*N*-oxyl (**ACT, Fig. 3a**). This reaction was selected for anode characterization studies because one-electron reduction of **ACT**⁺ to the aminoxyl **ACT** exhibits good electrochemical kinetics and thus will not limit anodic performance. The mediated anode was designed with two separate flow loops sharing a common liquid reservoir. The hydrogenation loop includes a packed-bed reactor containing Pd/C and is used to support continuous hydrogenation of **AQS** to **AQSH₂**. The electrolysis loop circulates the mediator/electrolyte solution over the anode, resulting in electrochemical oxidation of **AQSH₂** to **AQS**. This mediated

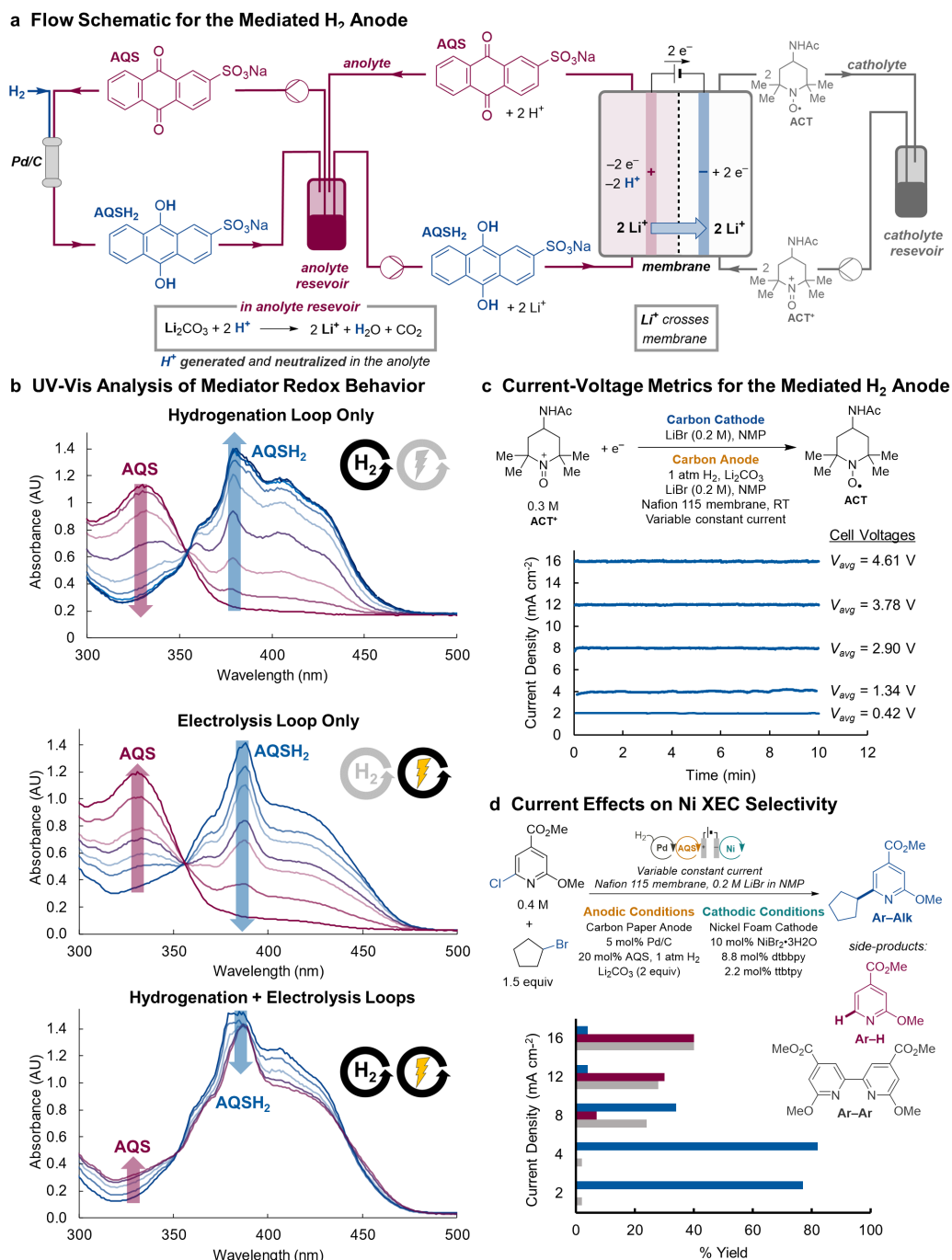


Fig. 3. Quinone-mediated H₂ anode flow cell. (a) Schematic diagram of the mediated H₂ anode flow system, integrating a hydrogenation loop with a packed-bed reactor for AQS hydrogenation and an electrolysis loop interfaced with a parallel-plate reactor for anodic oxidation of AQSH₂. (b) Analysis of redox states of the quinone mediator in the anolyte reservoir, using *in situ* UV-visible spectroscopy, while circulating only through the hydrogenation loop, only through the electrolysis loop, and through both the hydrogenation and electrolysis loops. (c) Operation of the mediated hydrogen anode shows stable cell voltage at current densities well beyond that needed to support Ni-catalyzed cross-electrophile coupling (XEC). (d) Assessment of Ni XEC product selectivity at different current densities. Optimal yield and selectivity are obtained at 4 mA/cm².

anode design provide a unique opportunity to manage protons generated during electrochemical oxidation of **AQSH₂**. The protons are retained in flowing solution, rather than passing through the membrane, and they are transported back into the anolyte reservoir where they undergo neutralization by Li₂CO₃. This neutralization exchanges H⁺ with Li⁺ ions in solution and results in the transport of lithium ions rather than the protons through the Nafion membrane during electrolysis. Inductively coupled plasma - optical emission spectrometry (ICP-OES) analysis of the catholyte solution during operation of the mediated H₂ anode showed a linear increase in [Li⁺], with a magnitude that directly correlates with the charge passed during electrolysis (**Fig. S12**). This feature contrasts conventional H₂ anode configurations, which are designed to ensure efficient proton transport through the membrane to support O₂ reduction or other cathodic reactions. In the present system, proton migration would have a deleterious effect, resulting in parasitic H₂ evolution at the cathode and/or generating undesirable byproducts via protonolysis of organometallic Ni intermediates (see Section 1 of the Supplementary Information). Thus, the mediated H₂ anode enables the use of H₂ as a source of electrons – without protons – for the cathodic reduction reaction.

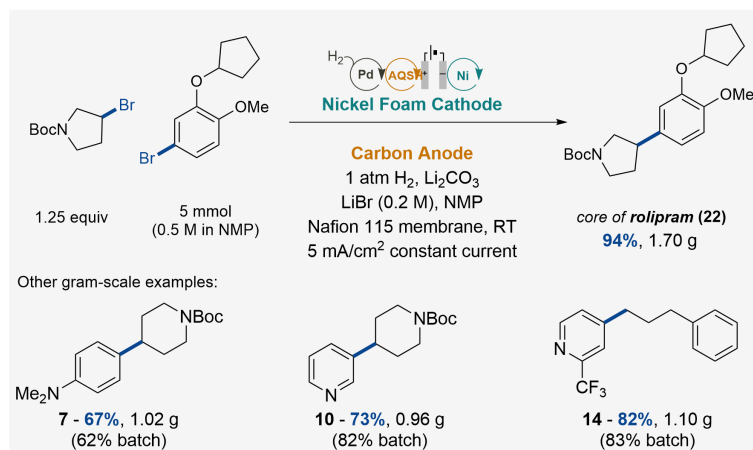
To monitor the interplay between the hydrogenation and electrolysis loops, *in situ* UV-visible spectroscopy was used to follow redox speciation of the quinone mediator in the anolyte reservoir. Operation of the hydrogenation loop without electrolysis leads to full reduction of the **AQS** to **AQSH₂** (**Fig. 3b**, hydrogenation loop only), with an isosbestic point at 355 nm. Ceasing flow in the hydrogenation loop and initiating the electrolysis loop while applying 5 mA current at the anode shows regeneration of **AQS**, while maintaining the isosbestic point (**Fig. 3b**, electrolysis loop only). When both loops are operating, the anolyte reservoir reaches a steady-state **AQS/AQSH₂** ratio that reflects the balanced rates of the chemical and electrochemical reactions (85% **AQSH₂** state of charge for the conditions shown in **Fig. 3b**, hydrogenation + electrolysis loops). Stable cell voltages were observed at current densities of 2–16 mA cm⁻² (**Fig. 3c**), extending beyond the current densities determined to be necessary to support optimal performance of Ni-

catalyzed XEC at the cathode (**Fig. 3d**). Analysis of the yields and selectivities of the Ni-catalyzed XEC reaction showed that optimal results with the indicated substrate were obtained at a current density of ~ 4 mA/cm².

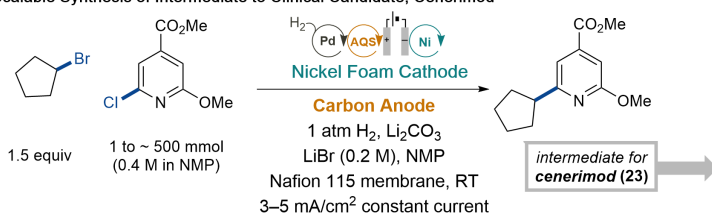
The mediated H₂ anode was then evaluated in larger-scale applications of Ni-catalyzed XEC using flow electrolysis methods. A 5 cm² parallel-plate flow reactor was used to synthesize several compounds on gram scale (**Fig. 4a**). The core structure of the antidepressant medication rolipram³⁵ was obtained in 94% isolated yield (1.7 g) using this method. In addition, several candidates from batch screening were investigated, prioritizing examples previously shown to be challenging with a Ni-catalyzed XEC process using sacrificial amine reductants.²⁹ These gram-scale reactions proceeded in 15–30% higher yields than those obtained previously (for context, see section 6 in the Supplementary Information). The origin of the improvement is not yet understood; however, the positive results highlight the merits of this H₂-driven electrolysis method.

Gram-scale synthesis of an intermediate to the Phase III clinical candidate, cenerimod³⁶, was similarly effective (**Fig. 4b**). An 82% product yield was obtained in a batch H-cell, and no loss of yield was observed upon transition to the gram-scale flow reactor. The flow conditions were then translated into a larger-scale commercial parallel-plate reactor that featured a stack of four membrane-electrode units with a total electrode surface area of 1600 cm² (see section 9 in the Supplementary Information). A current density of 4 mA/cm² was retained in the larger reactor, and the reaction proceeded 71% yield (without optimization). The flow reactor applications show the stable operation of the H₂ anode and Ni XEC flow cell over 4–16 h of operation, and the total current of 6.4 A applied in the large-scale demonstration would be sufficient to deliver approximately 0.5 kg/day of the cross-coupled product.

a Gram-Scale Syntheses, Including Intermediate to Active Pharmaceutical Ingredient, Rolipram



b Scalable Synthesis of Intermediate to Clinical Candidate, Cenerimod



H-Cell Batch	Gram-Scale Flow	Large-Scale Flow
20 h, 4 mA	16 h, 20 mA	4 h, 6.4 A
0.82 mmol	4.1 mmol	345 mmol
193 mg	0.965 g	81 g
82% yield	82% yield	71% Yield

Fig. 4. Scalable demonstration of the mediated H₂ anode to prepare molecules of pharmaceutical interest. (a) Gram-scale Ni-catalyzed XEC using a small parallel-plate flow reactor (5 cm² electrode surface area) to synthesize molecules including an intermediate to the drug, rolipram. (b) Synthesis of an intermediate to the drug, cenerimod, in three different formats: an H-cell batch reactor, a small parallel-plate flow reactor (5 cm² electrode surface area), and a large parallel-plate flow reactor (1600 cm² electrode surface area). See sections 8 and 9 in the Supplementary Information for full reaction conditions and experimental details.

Hydrogen represents an ideal, sustainable alternative to stoichiometric metal-based reductants, and the quinone-mediated H₂ anode system outlined herein establishes a unique strategy to achieve this goal for Ni XEC reactions. This mediated H₂ anode concept, however, should be applicable to many other applications. Electrochemistry provides a means to amplify the reducing power of H₂, allowing H₂ to serve as a source of electrons even when it lacks the intrinsic chemical potential needed to generate highly reduced catalytic intermediates. The quinone mediator serves as a versatile hydrogen carrier, and pairing catalytic hydrogenation of the quinone mediator with electrochemical oxidation of the hydroquinone enables efficient net electrochemical oxidation of hydrogen under non-aqueous conditions. Finally, the recirculating-flow mediated anode offers unique flexibility in proton management that differs from other H₂ anodes, such as fuel cell MEAs

or GDEs. Protons derived from hydroquinone oxidation are readily retained in the anode compartment, where they can be neutralized and replaced with lithium ions, thereby allowing H₂ to serve as a proton-free source of electrons for the cathodic reaction. Each of these features has important implications for future development H₂-driven electrosynthetic reduction reactions.

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Author contributions:

SSS, JBG, JT, and MRJ were involved in conceptualization of the project. Lab-scale efforts were conducted by MRJ, JT, VS, MCF, JBG, SMMK, and LW. Large-scale efforts were conducted by CB, DL, FL, TPV, MWD, JT, and MRJ. This project was completed under supervision of SSS, TWR, DJW and supported by funding acquired by SSS, TWR, DJW, CMH, and NAS. Manuscript writing was led by SSS, MRJ, and JT, with contributions from all authors.

Competing interests: A patent application describing a mediated H₂ anode has been filed.

Additional Information:

Supplementary information is available for this paper.

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