Electrolytic Conversion of Nitro Compounds into Amines in a Membrane Reactor

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ABSTRACT: Aromatic and aliphatic amines are key intermediates in the synthesis of pharmaceuticals, dyes, and agrochemicals. These amines are often sourced from nitro compounds. The hydrogenation of nitro compounds into amines requires harsh reaction conditions (e.g., high pressures and/or high temperatures) or additives that are usually toxic. Here we demonstrate hydrogenation of nitro compounds into amines in the hydrogenation compartment of a membrane reactor. The hydrogen is sourced from water in an adjacent electrolysis compartment, separated by a hydrogen-permeable palladium membrane. Modifications of the palladium membrane with catalysts enabled a wide range of commercially relevant nitro compounds to be hydrogenated into amines without any additives at ambient pressure and room temperature. This membrane reactor also enables nitro hydrogenation to occur at high concentrations and with high functional group tolerance.

INTRODUCTION

The hydrogenation of nitro compounds to amines is used across many industries[1]; for example, aromatic amines (e.g., aniline and derivatives) are used in pharmaceuticals, dyes, and agrochemicals.[2,3] Unfortunately, the conversion of nitro compounds to amines is carbon intensive and wasteful.[4,5] A method to selectively convert nitro compounds to amines at mild reaction conditions would assist the pharmaceutical, textile, and agricultural sectors to be more environmentally sustainable.

To date, very few hydrogenation methods have been reported that can reduce a wide range of nitro compounds into amines. In 2013, Beller and coworkers provided the first demonstration of a hydrogenation method with high functional group tolerance for a large reactant scope.[6] They accomplished this goal using nanoscale, carbon-supported iron oxide to catalyze the chemoselective hydrogenation of structurally diverse aromatic nitro compounds. While their demonstration represents the first universal method for nitro-to-amine reduction, the method requires high hydrogen pressures (p_{H2} = 5 MPa) and temperatures (T = 120 °C) and is restricted to reactant concentrations in the millimolar range.

To address these shortcomings, a number of alternative strategies have been considered.[3,7–13] Most of these strategies require $H_{2(g)}$, in reactors that operate at high pressures or temperatures.[6,14–22] To bypass the use of $H_{2(g)}$, catalytic transfer hydrogenation or hydride transfer reduction can be performed with additives that act as indirect hydrogen sources, such as HCOOH, N_2H_4, $NaBH_4$, or R_nSiH_{4-n}.[3,23] However, these protocols often require dry, inert atmospheres, are difficult to scale, and have issues related to catalyst degradation, product isolation, and reaction control.[3,7,9–12,23–27]

Electrochemical techniques can also drive nitro-to-amine reduction without $H_{2(g)}$.[28–30] While electrocatalytic hydrogenation can be performed at ambient conditions (e.g., atmospheric pressure, room temperature) with high reaction control and tunable selectivity, all reported methods only work at low reactant concentrations. These methods also all require additives and supporting electrolytes, which diminish process efficiency and scalability. Moreover, the catalysts do not survive long enough to be commercially viable.[31,32]

Here, we show a palladium (Pd) membrane reactor that can mediate functional group tolerant nitro-to-amine reduction at atmospheric pressure, room temperature, and high reactant concentrations. This membrane reactor sources hydrogen from water in an electrolysis compartment, then delivers reactive hydrogen species through a hydrogen-permeable Pd foil/membrane to an adjacent hydrogenation compartment to hydrogenate nitro compounds to amines. The reactions occur at ambient pressure and room temperature,[33,34] without any $H_{2(g)}$ supply or additives (Figure 1). Moreover, this membrane reactor converts nitro compounds to amines at high concentrations, which increases the probability of this conversion being done at scale.

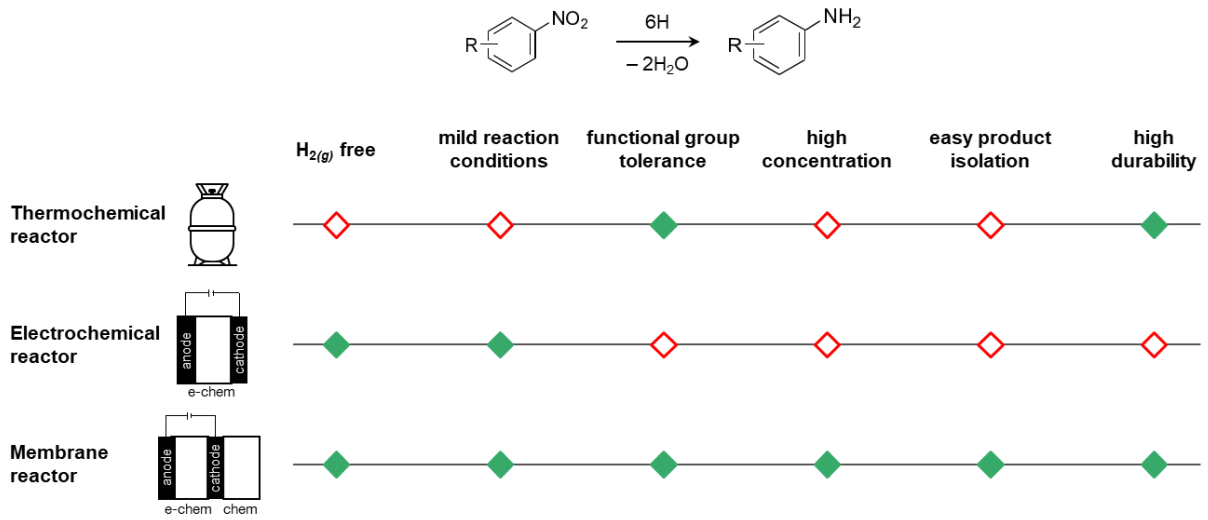


Figure 1. Reaction conditions and reactivities for thermochemical, electrochemical, and membrane reactors designed to hydrogenate nitro compounds to amine products. The membrane reactor is the only method that achieves high functional group tolerance at high concentrations while offering ease of product isolation and high durability. The membrane reactor also does not require $H_{2(g)}$ or additives (not shown). Solid green diamonds: demonstrated; hollow red diamonds: not demonstrated.

RESULTS AND DISCUSSION

The key component of the membrane reactor is a thin 25-μm Pd foil. This foil acts as a hydrogen-permeable membrane and cathode that physically separates the electrolysis compartment (containing an aqueous electrolyte) from the hydrogenation compartment (containing a solution of nitro compounds dissolved in an organic solvent).[33,35] In the electrolysis compartment, the oxidation of water generates protons (H^+). These H^+ are reduced at the surface of the Pd foil, diffuse through the Pd lattice, and then react with the organic nitro compounds in the hydrogenation compartment (Figure 2).[33,36,37] This architecture enables electrochemical and hydrogenation reactions to occur in separate compartments with different solvents and independently adjusted parameters. The top of the electrolysis compartment features small inlets to insert counter and reference electrodes. The top of the hydrogenation compartment features openings to sample the reaction solution during a hydrogenation reaction (Figure 2).

To perform the electrocatalytic hydrogenation reactions, we filled the electrolysis compartment with an aqueous solution of sulfuric acid (1 M H_2SO_4), which served as electrolyte for enhanced water oxidation. The hydrogenation compartment was filled with a solution of 0.05 M of a nitro compound dissolved in an organic solvent. Electrolysis was performed for 4 hours at a constant current density of 100 mA cm^{-2} (where area corresponds to the geometric surface area of one face of the Pd foil/membrane). The reactor and solvents were at ambient pressure and room temperature. We monitored the reaction products using ^1H NMR spectroscopy and gas chromatography-mass spectrometry (GC-MS).

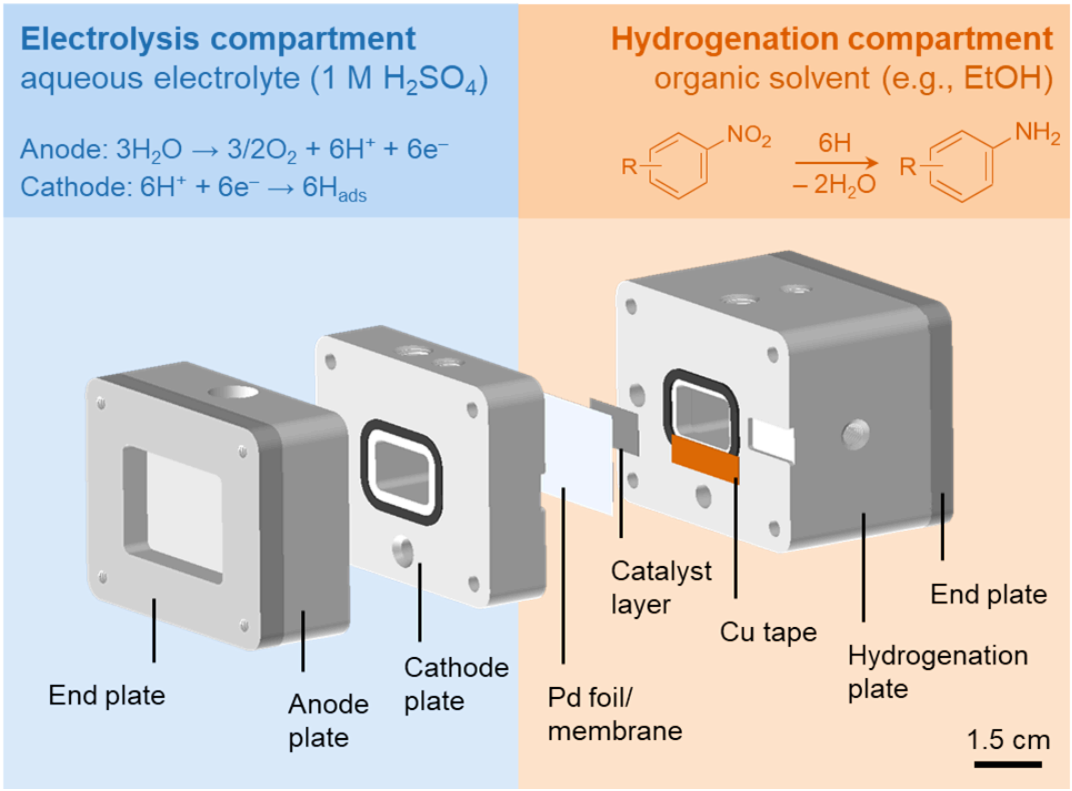


Figure 2. Expanded view of a Pd membrane reactor for electrolytic hydrogenation of nitro compounds to amines. In the electrolysis compartment (blue) of a membrane reactor, a positive bias drives the oxidation of water at an anode to form H^+, which migrates to the Pd foil that acts as a cathode and hydrogen-permeable Pd membrane. The H^+ are reduced at the Pd foil, then migrate through the Pd foil, and then react with nitro compounds in the hydrogenation compartment (orange) to form amines.

First, we attempted to hydrogenate 0.05 M of nitrobenzene dissolved in ethanol (entry **1**, Table 1). We used a bare Pd foil and observed no aniline formation after 4 hours of hydrogenation (Figure S1). We then used a Pd foil containing an electroplated Pd-black layer facing the hydrogenation compartment (Pd|Pd-black),[38] because the high surface area of a Pd-black layer increases catalytic activity in a membrane reactor.[33,39] The Pd|Pd-black membrane mediated the hydrogenation of nitrobenzene to aniline in a good yield (91%) over 4 hours of hydrogenation (Figure S2). We also tested electrodeposited Ru and Rh catalyst layers on Pd foils (i.e., Pd|Ru and Pd|Rh membranes), but both were inferior to the Pd|Pd-black membrane (Figure S2).

Next, we studied the hydrogenation of other nitro compounds, such as 4-nitroanisole (entry **2**, Table 1). We observed that the Pd|Pd-black membrane was not universally effective (Figure S3). We introduced additional catalyst layers with well-dispersed, carbon-supported metal nanoparticles onto the Pd|Pd-black membrane. This strategy yielded positive results; for example, we spray-coated commercial Pd/C powder (with a hydrophobic PTFE binder) onto the Pd|Pd-black membrane to form a "Pd|Pd-black|Pd/C" membrane. This membrane enabled full conversion of 4-nitroanisole to 4-methoxyaniline (entry **2**) over 4 h of hydrogenation. Both the Pd foil and Pd|Pd-black membrane yielded significantly less hydrogenated product under the same conditions.

We then tested the broad reactant scope of hydrogenation chemistries with the catalyst-coated membranes, using compounds relevant to the pharmaceutical industry as a case study (entries **3**–**10**, Table 1; Figures S4–S19). We synthesized sulfanilamide (entry **6**, Table 1; Supplementary Figs. 10 and 11), 4-aminophenol (entry **7**, Table 1; Figures S12, S13), and 3-fluoro-4-morpholinoaniline (entry **8**, Table 1; Figures S14, S15) in high purities and quantities.

These compounds serve as antibacterial drugs (entry **6**)[40] or as valuable precursors for sulfa drugs (entry **6**)[41], paracetamol (entry **7**)[42], and linezolid (entry **8**)[43]. We also selectively hydrogenated flutamide (entry **9**, Table 1; Figures S16, S17), a drug used to treat prostate cancer, whose hydrogenated form is more compatible with the human body.[44–46]

While these studies demonstrate the wide reaction scope of the membrane reactor, a particularly noteworthy conversion in the membrane reactor is the selective conversion of nitrobenzene to aniline over a wide range of concentrations (0.05–2.00 mol L^{-1}; Figures 3, S20). We are not aware of another technique that enables functional group tolerant nitro-to-amine reduction at such high concentrations, high reaction control, and ease of product isolation. To demonstrate the power of the membrane reactor, we carried out a similar experiment in a conventional electrochemical H-cell, where a Pd|Pd-black|Pd/C cathode immersed in 0.005 M nitrobenzene in 1 M H_2SO_4 was separated from the anode compartment (Pt anode in 1 M H_2SO_4) by a cation exchange membrane. This experiment in the H-cell did not yield any nitrobenzene conversion (Figure S21).

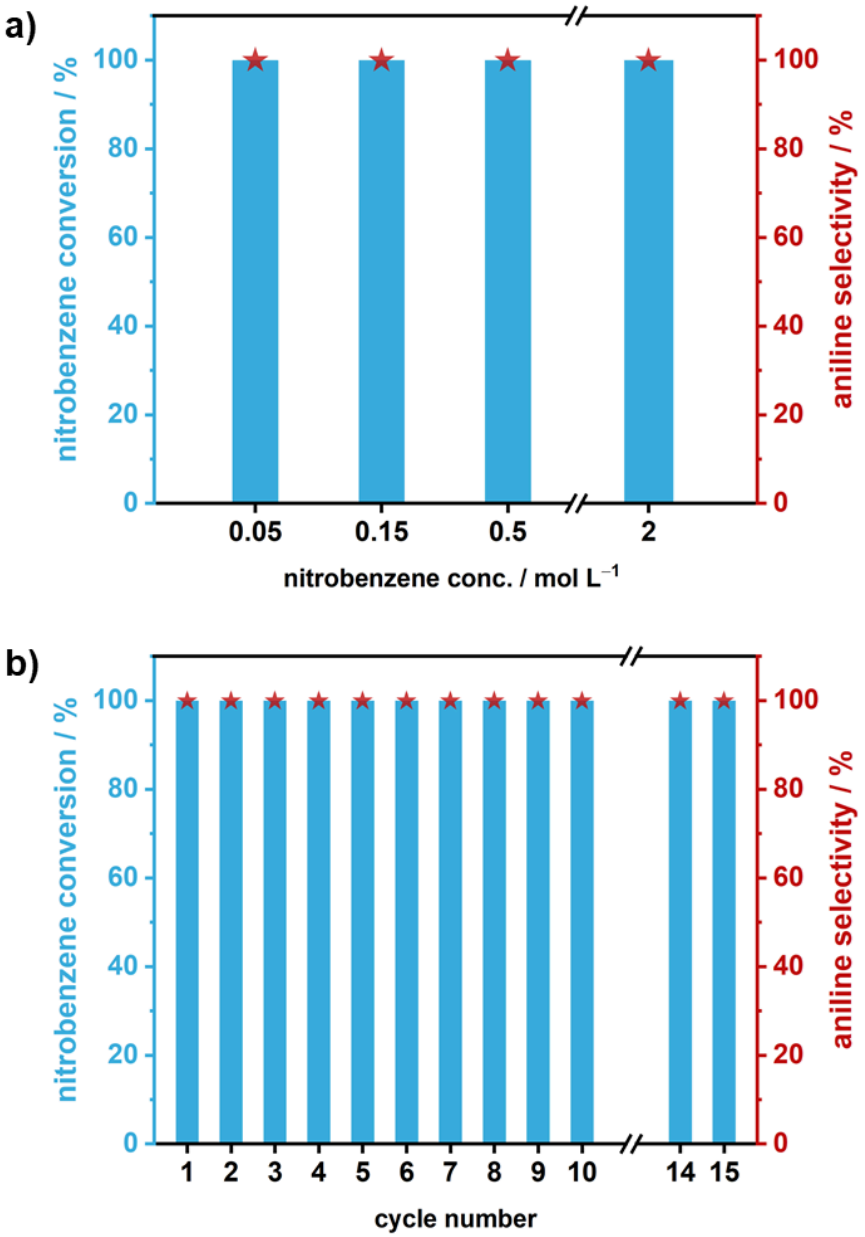
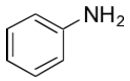
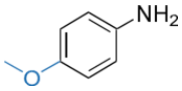
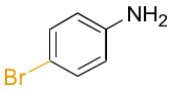
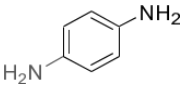
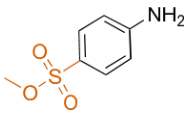
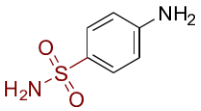
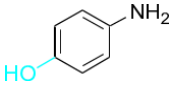
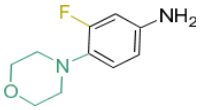
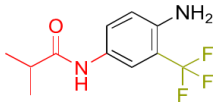


Figure 3. Membrane reactor conversion and selectivity for nitrobenzene to aniline hydrogenation. (a) The amount of nitrobenzene converted to aniline (entry **1**, Table 1) in a membrane reactor as a function of initial nitrobenzene concentration. The reaction was performed at ambient pressure, 20 °C, and 100 mA cm^{-2} using a Pd|Pd-black|Pd/C membrane, and with EtOH solvent and H_2SO_4 electrolyte in the hydrogenation and electrolysis compartments, respectively. (b) Repeated electrolysis experiments at a current density of 200 mA cm^{-2}, where each 2-hour cycle was performed in galvanostatic mode using a reactant concentration of 0.05 mol L^{-1}. After every second cycle, the reactor was disassembled and the Pd|Pd-black|Pd/C electrode was de-loaded at a cell potential of +0.5 V. The percent conversion of nitrobenzene and the product selectivity for aniline are indicated by the blue bars and red asterisks, respectively.

Table 1. Listing of Hydrogenation Reactions Converting Nitro Compounds into Amines in a Membrane Reactor, All at Ambient Pressure and Room Temperature.[a]

entry	product	reaction time / h	reactant conversion / %	product selectivity / %	main application fields
1		4	>99	>99	polymers, fine chemicals
2		4	>99	>99	textiles (azo dyes)
3		4	>99	>99	pharmaceuticals, textiles (azo dyes)
4		4	>99	>99	polymers, textiles (azo dyes)
5		4	95	95	textiles (azo dyes)
6		4	95[b]	>99	pharmaceuticals (antibacterial sulfa drugs)
7		4	83[c]	>99	pharmaceuticals (acetaminophen drug precursor)
8		15	>99[d]	95	pharmaceuticals (linezolid drug precursor)
9		17	95	>99	pharmaceuticals (anti-androgen drugs)
10		4	>99[e]	>99	pharmaceuticals, agrochemicals

[a]Reaction conditions: Pd|Pd-black|Pd/C membrane, 20 °C, 100 mA cm^{-2}, 0.05 mol L^{-1} reactant in EtOH (unless otherwise stated); [b]Isolated product yield: 94%; [c]solvent mixture: 4:1 EtOH:H_2O (v:v), isolated product yield: 80%; [d]isolated product yield: 94%; [e]solvent: cyclohexane, isolated product yield: 95%.

The membrane reactor was also durable on the timescale of our laboratory experiments. We performed 15 successive 2-hour hydrogenation cycles using the same Pd|Pd-black|Pd/C membrane at a current density of 200 mA cm^{-2}, with no signs of degradation. All 15 runs yielded excellent conversion (>99%) and selectivity (>99%) for each cycle (Figures 3, S22–S24).

We were able to manipulate the reactivity in the membrane reactor in multiple ways. For example, the thickness, surface area, and loading of the Pd/C catalyst layer impacted reactivity (Figures S25, S26). A thicker Pd/C layer increases the electrochemical surface area (ECSA) to increase the rate of hydrogenation (Figure S27). However, at exceedingly high thicknesses, the mechanical stability of the membrane and the adhesion of the catalyst layer to the Pd foil are drastically reduced. We set out to optimize this trade-off in Pd/C layer thickness. When we increased the ECSA for a Pd|Pd-black|Pd/C membrane by about 200- and 3-fold relative to a bare Pd foil and Pd|Pd-black membrane, respectively (Figure S27), we were able to maintain a high hydrogen permeability for a Pd|Pd-black|Pd/C membrane, despite the presence of hydrogen-impermeable carbon support and PTFE binder (Figure S28).

Contact angle measurements reveal the Pd|Pd-black|Pd/C membrane was also more hydrophobic than a bare Pd foil and a Pd|Pd-black membrane (Figure S29). We attribute this difference to the presence of the hydrophobic PTFE binder in the Pd/C catalyst layer. We conjecture that this feature also helps increase the rate of hydrogenation of nitro compounds in the membrane reactor.[47,48]

Nitrobenzene, an unsubstituted nitroarene, could be hydrogenated with both Pd|Pd-black and Pd|Pd-black|Pd/C membranes, but substituted nitroarenes could only be hydrogenated with the Pd|Pd-black|Pd/C membrane (Figures 3, 4, S2, S24–S26). On this basis, we assert that the

polycrystalline Pd nanoparticles (with average crystallite sizes of 18 nm; Figure S29) are important for mediating hydrogenation of substituted nitroarenes.

The importance of the Pd nanoparticles in governing reactivity prompted us to evaluate other catalysts coated on the Pd-black layer. For this phase of the study, we selected the hydrogenation of 4-nitroanisole as a model reaction, and tested membranes containing different spray-coated layers of Ru/C, Rh/C, and Pt/C. These metals were selected because they are widely known hydrogenation catalysts.[16,20,21,27,49,50] Each of these metals improved hydrogenation reactivity by at least 3-fold relative to the Pd|Pd-black membrane. Notwithstanding, the most effective membrane was Pd|Pd-black|Pd/C, which mediated 100% conversion over 4 hours of electrolytic hydrogenation (Figures 4, S30).

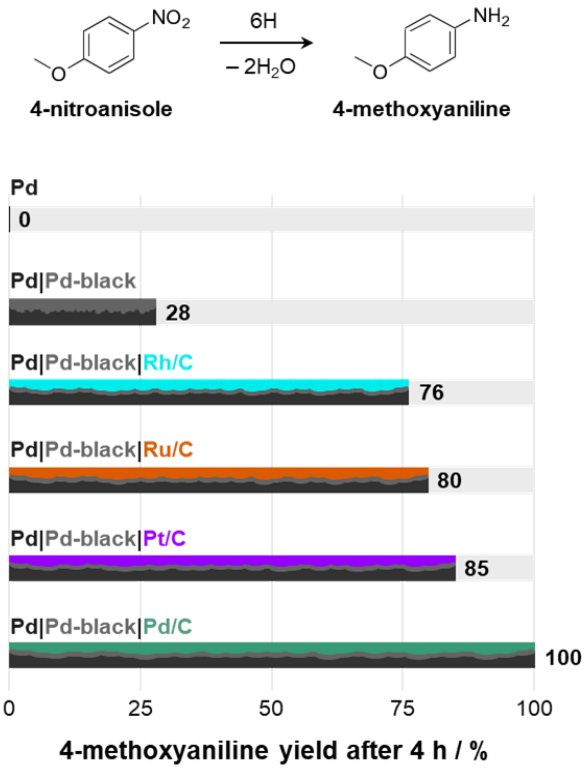


Figure 4. The amount of 4-nitroanisole converted to 4-methoxyaniline in a membrane reactor for different metal catalyst-coated membranes. The reaction was performed at ambient pressure, 20 °C, 100 mA cm^{-2}, and a reactant concentration of 0.05 mol L^{-1} using EtOH as solvent in the hydrogenation compartment. The percent yield of 4-methoxyaniline is indicated by the horizontal bars. All metal catalyst-coated membranes achieve higher percent yields for 4-methoxyaniline than a bare Pd foil and a Pd|Pd-black membrane.

The hydrogenation of nitrobenzene can proceed through either a "direct pathway" or an "indirect pathway" (Figure 5). Both pathways pass through a nitrosobenzene intermediate, which is in equilibrium with its dimer, azobenzene dioxide.[51,52] In solution, the monomeric nitrosobenzene can be assumed predominant.[52,53] For the direct pathway, this nitrosobenzene intermediate is reduced to phenylhydroxylamine, which is subsequently reduced to the aniline product.[54] For the indirect pathway, the phenylhydroxylamine intermediate instead undergoes intermolecular condensation with nitrosobenzene to form azoxybenzene, which is reduced to azo- and hydrazobenzene, and then to aniline. We performed hydrogenation experiments with nitrobenzene dissolved in each of EtOH and MeOH, and tracked the reactants, intermediates, and products as a function of electrolysis time using *ex situ* ^{1}H NMR spectroscopy and GC-MS (Figures 5, S31, S32). When using EtOH, we observed the formation of nitrosobenzene and aniline. We did not detect azobenzene dioxide or phenylhydroxylamine, nor did we observe the azoxy-, azo-, and hydrazobenzene intermediates (Figures 5, S31). After 4 hours of hydrogenation in EtOH, we observed full conversion to aniline (>99%). We thus hypothesize a direct pathway using EtOH in the hydrogenation compartment. When we performed the same experiment with MeOH, we observed the formation of nitroso-, azoxy-, and azobenzene intermediates (Figure S32). After 4 hours of hydrogenation in MeOH, a low yield (13%) of aniline had formed, along with nitroso-, azoxy-, and azobenzene intermediates. These results are consistent with the condensation reaction of nitrosobenzene and phenylhydroxylamine being faster in MeOH than in EtOH, or the hydrogenation of phenylhydroxylamine could also be slower in MeOH.[54,55]

Notably, the combination of a Pd|Pd-black|Pd/C membrane and the use of EtOH solvent in the hydrogenation compartment suppressed the formation of side products over a wide

concentration range. This achievement is significant because byproducts are often observed in related hydrogenation reactions.[56–58]

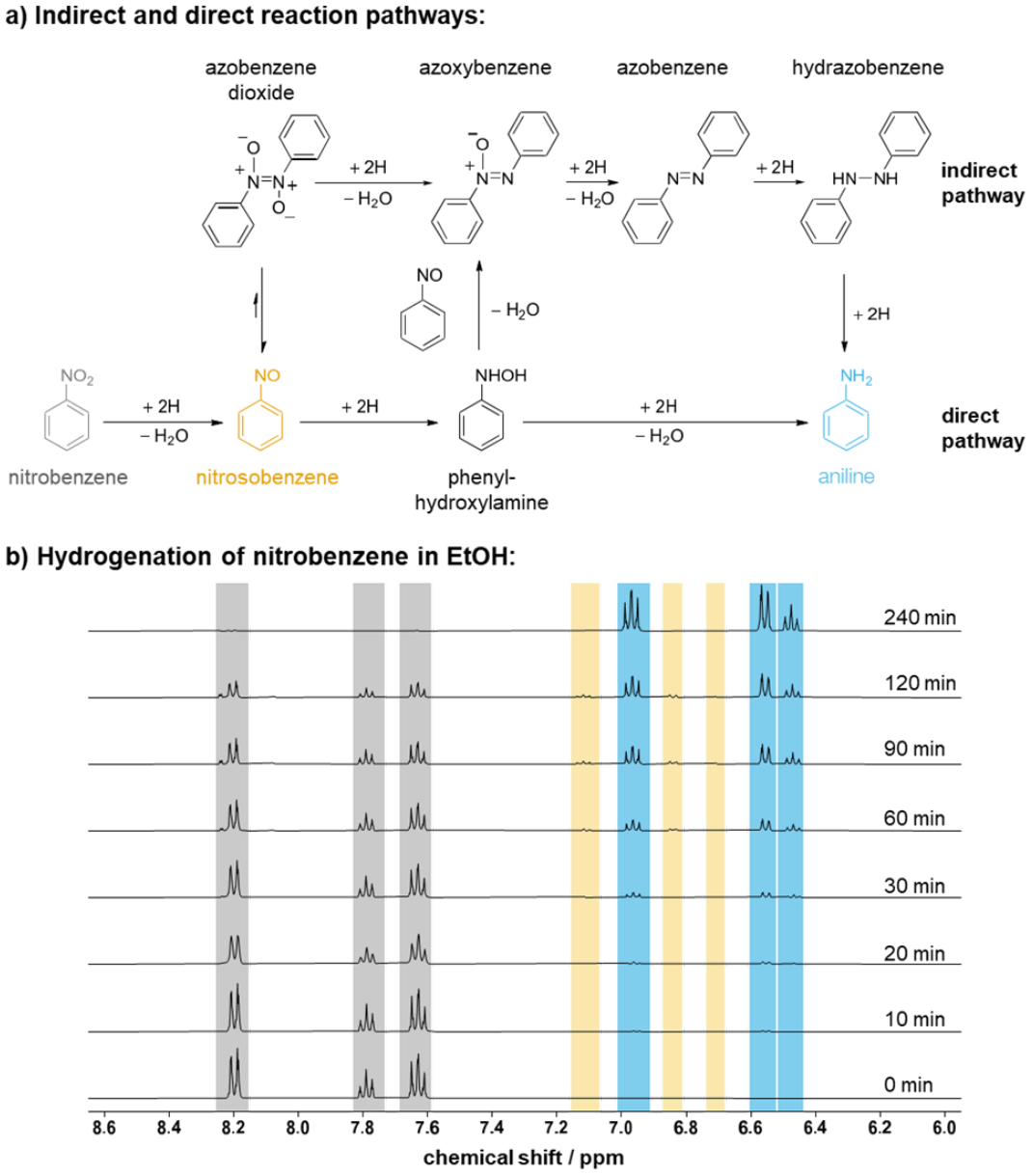


Figure 5. Hydrogenation of nitrobenzene to aniline in EtOH. (a) Direct and indirect pathways for the hydrogenation of nitrobenzene to aniline. (b) Temporal monitoring of hydrogenation of 0.5 mol L^{-1} nitrobenzene in EtOH, as a function of electrolysis time, by ^{1}H NMR spectroscopy. A Pd|Pd-black|Pd/C membrane was used for hydrogenation in a membrane reactor at ambient pressure, 20 °C and 100 mA cm^{-2}.

CONCLUSION

This work demonstrates how a membrane reactor can be used for functional group tolerant hydrogenation of nitro compounds to amines with electrolytically sourced hydrogen under mild reaction conditions. This previously undemonstrated approach to nitro hydrogenation overcomes challenges related to conventional hydrogenation, such as high partial pressure of $H_{2(g)}$, high temperature, low reactant concentration, and byproduct formation.

ASSOCIATED CONTENT

The Supporting Information is available free of charge on the ACS Publications website. Detailed experimental procedures, membrane reactor setup, characterization of membranes and catalyst-coated membranes, characterization of compounds, ^{1}H NMR and GC-MS spectra, XRD patterns, ECSA evaluations and additional electrochemical data (PDF)

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Author contributions

A.S.H. and M.L.F. contributed equally. A.S.H., M.L.F. and C.P.B. conceived the idea of the study. A.S.H. and M.L.F. conducted the experiments and evaluated the data. Y.W. carried out XRD measurements. M.D.S. contributed to electrode design and electrochemical characterization techniques. All authors jointly wrote the manuscript and have given approval to the final version of the manuscript.

Notes

The authors declare no competing interests.

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