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A Mechanistic Perspective on the Mechanochemical Method To Reduce Carbonyl Groups with Stainless Steel and Water

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Mechanochemistry through high-speed ball milling has become an increasingly popular method for performing organic transformations. This newfound interest in high-speed ball milling is in part driven by the benefit of performing reactions in the absence of solvent. Mechanochemical reactions are often conducted in stainless-steel vials with stainless-steel balls. Since stainless steel is made of several readily oxidizable metals (Fe, Cr, and Ni), reduction reactions using water as a hydrogen source were explored using a temperature-controlled mixer mill. Mechanistic studies suggest that the reduction proceeds via a single electron transfer (SET) pathway, with iron and nickel being essential components for the reaction.

Introduction

An area of research that is crucial for organic synthesis is the reduction of unsaturated bonds, and of particular interest is the reduction of carbonyl groups to the corresponding alcohols.[1] There are several ways to achieve this transformation using either non-metal,[2] or metal-based reagents, where heterogeneous[3] or homogeneous catalysis[4] can play significant roles. For the two types of catalytic methods, transition metals are typically used, and either direct hydrogenation or transfer hydrogenation is employed.[5] Transfer hydrogenation may be preferred due to the safety concerns of using dihydrogen, particularly under high pressures. Furthermore, mild conditions including low or moderate pressures and temperatures, especially when applied to processes such as biomass valorization, are advantageous since highly-oxygenated biomass derivatives are prone to decomposition upon vaporization.[6] A burgeoning field of hydrogenation is using transition metals in the form of nanoparticles to facilitate reduction.[7] However, many of these systems require the use of either an expensive 2nd or 3rd- row transition metal or additional reducing agents such as hydrides.[8]

To make transfer hydrogenation reactions more attractive processes, water has been used as an additive or solvent to improve the reactivities of the hydrogen donors. For many of these reports, poor solubility of the reagents in water limited the reactivity.[9] Mechanochemistry, a technique relying on mechanical motions to facilitate chemical reactions, may be adopted to obviate the need to use the expensive 2nd/3rd-row transition metals while addressing the solubility issue of organic reagents in water. Zero-valent metals as unique materials like foil, rods, pellets, etc. have been used successfully in mechanochemical reactions.[10] Further, our group has demonstrated that reaction vials and balls used for mechanochemical media can act as catalysts and/or reagents for a number of organic transformations.[11] Other groups have since expanded this work, with Borchardt even publishing guidelines on best practices for the use of milling media as catalysts to help increase its impact on greener synthesis.[11f] This strategy has been expanded to encompass alloyed media like stainless steel. Of particular relevance to this work, Sawama, Sajiki and coworkers developed a novel procedure by which hydrogen gas was generated from water under planetary mechanochemical conditions using stainless steel as the reaction media.[12] The in-situ generated hydrogen was used to reduce a variety of unsaturated bonds under the same mechanochemical conditions.[13] Further modifications to the procedure (e.g., the use of diethyl ether or 2-propanol as the hydrogen source and/or Pt/C and Fe(0) as the catalysts) allowed benzene rings to be reduced to cyclohexyl rings.[14] Mechanistic insight revealed in these studies suggests that a single electron transfer (SET) pathway is responsible for reducing water to molecular hydrogen, leading to the hydrogenation of the unsaturated bonds. This conclusion may represent only planetary mill mechanochemical systems and does not necessarily provide insight into other mechanochemical systems, like shaker mills, which are also commonly used for synthesis.

Mechanochemistry may be facilitated by a number of equipment such as planetary mills, shaker mills, and twin-screw extruders.[15] Planetary mills operate at comparatively high temperatures due to the grinding of the mechanochemical

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media.[16] However, this is not the case for all other mechanochemical systems. In the original work by Sawama, Sajiki, and co-workers it was noted that the number of balls, equivalents of water, time, and most importantly rotation speeds had a significant effect on the yield of the reaction.[12] As an example, reduction of diphenylacetylene afforded 1,2-diphenylethane with a yield of 94% when milled at 800 rpm, but only 4% when milled at 650 rpm.[13] Additionally, when the reaction was conducted at 500 and 250 rpm, no product was detected. These reactions also give a range of products, where stilbene appears to be an intermediate along the reduction pathway. Having a better understanding of the energetics of the mechanochemical reaction provides the opportunity to increase selectivity and limit the number of variables that currently exist for this mechanochemical procedure to reduce unsaturated bonds. The primary aim of this work is to better understand the energetic requirements for this environmentally benign reduction reaction to take place. At present the results performed in the planetary mill are not easily extrapolated to mixer/mill or twin-screw extruder conditions. Additionally, we intend to (1) explore stainless-steel-mediated reduction for carbonyl groups using a temperature-controlled mixer mill, (2) identify the individual metals and metal combinations within stainless steel that are responsible for the reduction of carbonyl functionalities, and (3) better understand the mechanism by which this reduction occurs. These results are expected to have broader implications, including how electrochemistry may be applied to mechanochemical systems.

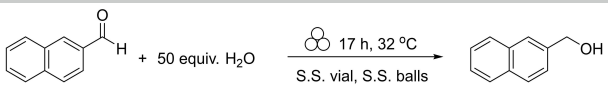
Results and Discussion

The first set of experiments for this work focused on reproducing Sawama and Sajiki's protocol in a SPEX8000M Mixer Mill to investigate if the conditions were translatable to a mixer mill. After milling the reaction of naphthaldehyde (**1 a**) for 3 h using 1 stainless steel ball, we observed no reduction of the aldehyde. Given the lack of reactivity, we assumed the mixer mill with 1 stainless steel ball could not provide the necessary energy to facilitate the reaction. Next, the impact of using different numbers of stainless-steel balls on the reduction of naphthaldehyde was studied under constant milling speed (60 Hz, Table 1). After milling the reaction for 17 h using 1 ball (entry 1), the system again failed to provide enough energy to yield product. When 7 stainless-steel balls were used, the reduction of **1 a** proceeded with a relatively high conversion to the corresponding alcohol (entry 2). Conducting the reaction using 18 stainless-steel balls resulted in a higher conversion to the corresponding alcohols (entry 3). These results support the notion that increasing the number of milling balls can produce different amounts of thermal energy. However, without a rigorous temperature control, it is difficult to determine if the differences observed are due to the metal source or the thermal energetics of the system.

A number of research groups, including ours, have begun to modify mixer mills to provide more strict and accurate temperature control. One of these efforts resulted in custom modifications to a SPEX8000M mixer mill, allowing the reaction vials to be heated to desired temperatures up to approximately 200 °C.[17] With this tool in hand, we aimed to vary the temperature of the mill to determine the relationship between temperature of the reaction with the milling speed observed by Sawama and Sajiki.

For the next set of experiments, we used a constant milling speed of 60 Hz (standard operating frequency on the SPEX8000M Mixer Mill) and adjusted the temperature of the mill to carry out the initial reduction. Previous work demonstrated that the vapor pressure of the reagents could have a significant effect on the rate of the reaction.[14a] Therefore, to minimize solvent effects and volatility issues, 2-naphthaldehyde (**1 a**) was again selected as the substrate for reaction optimization. Reduction of **1 a** to **2 a** using the combination of stainless steel and water in our system was best carried out at 90 °C (Figure 1) using 7 stainless-steel balls. The same conditions with just one stainless-steel ball resulted in no conversion, most likely because the oblique collisions were still necessary to activate the metal. The results were not reproducible for reactions performed at or above 100 °C. It is known that volatile gases can be difficult to react under mechanochemical conditions, therefore this irreproducibility is most likely due to

Table 1. Reduction experiments using different numbers of stainless-steel balls.



1a 2a

Entry[a]	Number of stainless-steel (S.S.) balls[a]	% Conversion[b]
1	1	0
2	7	74
3	18	84

[a] Stainless steel hardness is 440C. [b] Percentages are conversions calculated from ^{1}H NMR.

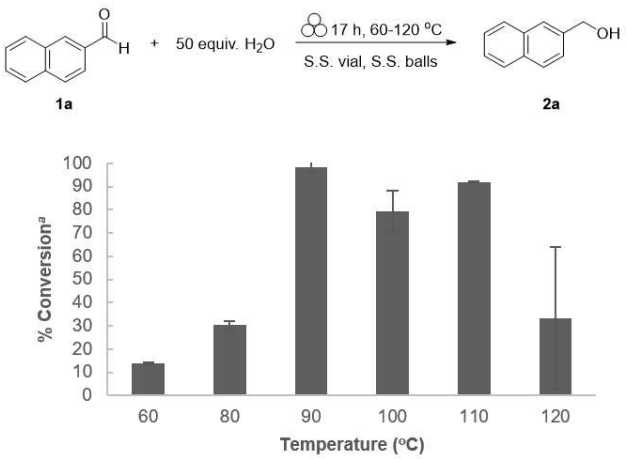


Figure 1. Optimization of temperature for stainless steel and water-assisted reduction of 2-naphthaldehyde ([a]Reported as an average of two runs). 7 S.S. balls were used.

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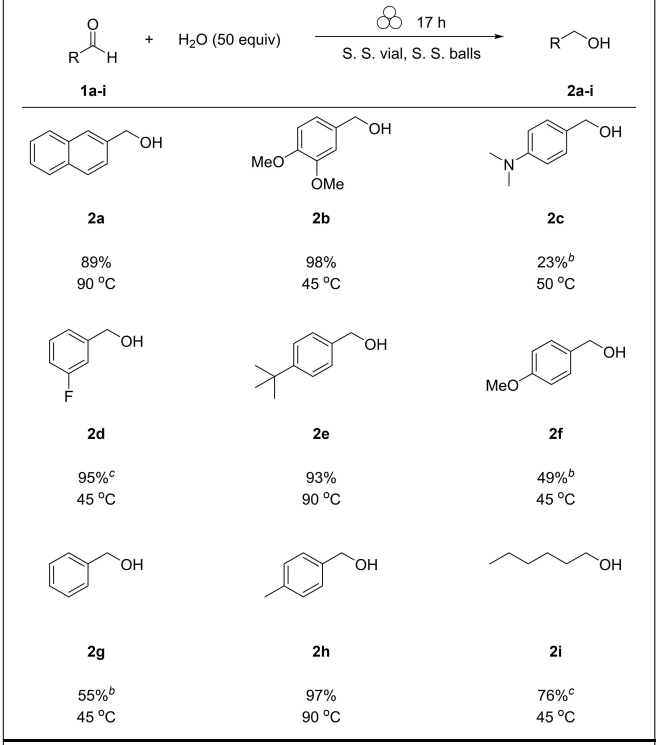
the vaporization of water.[18] Furthermore, at °C, the reduction occurred to both the carbonyl group and the aromatic ring, resulting in the formation of 1,2,3,4-tetrahydro-6-methylnaphthalene. This demonstrates that adjusting temperature can provide better control over the reaction energetics.

Once the optimal temperature was established to be 90 °C, additional optimization studies were performed to identify the ideal conditions for the reduction of aldehydes by stainless steel in a mixer mill. These optimization studies include the amount of water, time, and the type of stainless-steel material (fine shavings vs ball bearings). The details of the water and material optimization studies can be found in the Supporting Information. Notably, the kinetic profile (Figure 2) of the reaction shows that there is an induction period for the process and no substantial amount of product was observed until after 6 h. This induction period is most likely due to the time needed to generate a fresh surface of the stainless steel. At the end of each reaction, it was visually clear that metal particles from the stainless steel were present in the reaction mixture. It is hypothesized that the reaction proceeded once enough of the stainless-steel metal was activated from the surface of the vial/ball. Ultimately, it was found that the ideal conditions were to use 50 equivalents of water in comparison to the aldehyde substrate, a 17 h reaction time, and stainless-steel balls. To demonstrate that this methodology is effective for other aldehydes, a substrate scope was studied. These results are summarized in Table 2.

While **1a** was optimized to yield a high conversion at 90 °C, that was not the case for all substrates. Since the SPEX8000M Mixer Mill used for this work has the capability for temperature control, we were able to adjust the temperature based on the reaction energy needs of the substrate. Benzaldehyde (**1g**) underwent the water-assisted reduction with a quantitative conversion at 45 °C.[19] Alcohols **2b** and **2d** were obtained in high yield and high conversion at 45 °C. Substrates with electron-donating groups at the para position were slowly reduced at 45 °C (**1f**) or 50 °C (**1c**). Substrate **1f** is of particular note because its electron-donating group is a methoxy group, contrasting the result of **1b**, which was reduced in high yield at the same temperature. Weakly electron-donating groups such as tert-butyl and methyl groups were well tolerated at 90 °C, providing alcohols **2e** and **2h** in high yield (93% and 97%, respectively). An aliphatic aldehyde with a linear chain (**1i**) was also amenable to the conditions, with a moderate conversion of 76% observed at just 45 °C.

This methodology is not selective for substrates bearing halides; substrate **1j** yielded a small amount of aldehyde **1g** at 45 °C and a nearly quantitative amount of alcohol **2g** at 80 °C (Scheme 1). This dehalogenation process is not unprecedented, especially in the presence of nickel.[20] The nitro-substituted aldehyde (**1k**) also underwent other transformations in addition to reduction of the carbonyl group. Although the conversion of **1k** was low, the reaction mixture was comprised of the expected 4-nitrobenzyl alcohol (**2k**), 4-aminobenzaldehyde (**3k**) as a result of nitro reduction, and an azoxy compound analogous to a previously proposed intermediate during SET reduction of nitrobenzene.[21] The results here highlight the fact that adjusting the reaction environment to specific temperatures can provide us with a better opportunity to understand the mechanistic pathways of this reduction process, which was unavailable previously.

Table 2. Substrate scope for the reduction of aldehydes with stainless steel and water.[a]



[a] Reactions conducted in a stainless-steel vial with 7 stainless-steel balls (3/16"). Isolated yield unless noted otherwise. [b] NMR yield, using hexamethylbenzene as an internal standard. [c] Percent conversion determined by ^{1}H NMR spectroscopy.

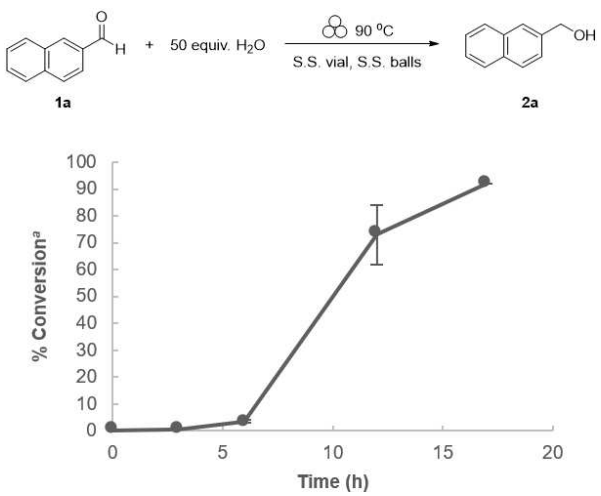


Figure 2. Reaction profile under the optimized conditions for stainless steel and water-assisted aldehyde reduction ([a]Reported as an average of two runs). 7 stainless steel balls were used.

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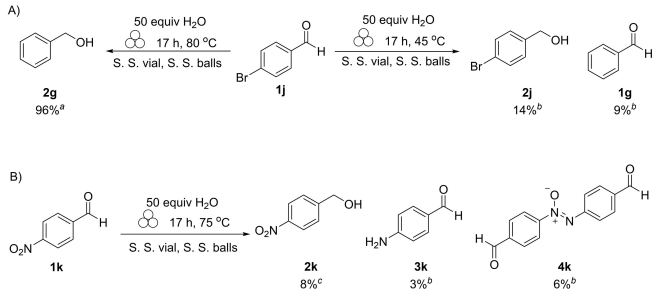


Scheme 1. Competing processes for the aldehyde reduction: (A) dehalogenation and (B) nitro reduction. [a] NMR conversion. [b] NMR yield. [c] Isolated yield.

Having established that a variety of aldehydes can be reduced mechanochemically using stainless steel and water at various temperatures, we were interested in following-up with Sawama and Sajiki's work to know if there was a particular metal responsible for the effectiveness of this alloy.[12] There are many types of stainless steel, and two common types are 304 and 440C. Their elemental compositions are outlined in Table 3.[22,23]

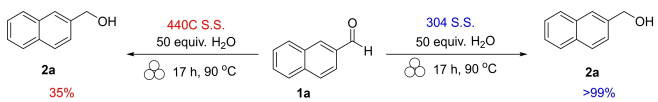
The primary differences between these two types of stainless steel are the mechanical properties (440C is "harder" than 304) and the nickel content. Stainless steel 440C is slightly more refined and contains no nickel. Sawama, Sajiki, and co-workers used stainless steel 304 in their study and hypothesized that chromium is essential for the reduction of water to H_2 while nickel plays the catalytic role for the hydrogenation process.[13] Given the assumption that nickel holds such an important role, a reaction vial made of 440C should have a different outcome than that made of stainless steel 304. We purchased vials and milling balls made from 440C stainless steel and compared them to our previous results which were obtained from using stainless steel 304. Reactions in two types of stainless steel were thus performed, and the conditions and results are summarized in Scheme 2. The reaction with the 440C-grade stainless steel showed a markedly lower conversion than that with the 304-grade stainless steel. However, a noticeable amount of **2a** was produced using 440C-grade stainless steel, indicating that iron and chromium may also work synergistically to reduce the unsaturated bonds. The 35% conversion was substantial enough to prompt further investigation into the role that the metals play for this process.

According to metal redox potentials,[24] iron should be less reactive than metals such as aluminum, manganese, zinc, and chromium for reducing carbonyl compounds via a SET pathway. However, the data in Table 4 contradict this hypothesis. To eliminate the influence of the metal from a stainless-steel jar and focus on the effect of added metal only, a Teflon® (PTFE) jar was used in our study. As shown in Table 4, all the metals more reducing than hydrogen in the electrochemical series resulted in the conversion of the benzaldehyde to benzyl alcohol except molybdenum because it requires high temperature to displace hydrogen in water. Copper and silver are less reducing than hydrogen (entries 8 and 9, respectively), and both metals did not facilitate the conversion of benzaldehyde to benzyl alcohol. These results are consistent with two mechanistic stages that might be involved in the reduction: SET between reactive metal and water to produce molecular hydrogen, followed by hydrogenation of the organic substrate on the metal surface. These results also agree with Sawama and Sajiki's work performed in a planetary mill, with the exception that in our analysis, iron (as opposed to chromium) appears to be the more prominent metal for the SET. It is important to note that milling balls of different materials produce different amounts of thermal energy, thus without accurate temperature control, it is difficult to determine if the differences observed is due to the metal source or the thermal energetics of the system.

To assess the involvement of SET and hydrogenation process, a series of mechanistic studies were conducted (Scheme 3). First, to confirm that the hydrogen originated from water, a reaction with D_2O instead of H_2O was performed, and the vial and balls were dried thoroughly prior to the reaction. Using the methyl resonance in **3h** for NMR integration, it was

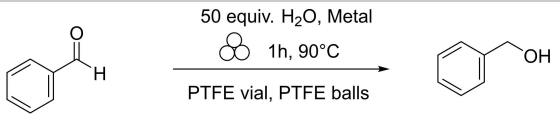
Table 3. Compositions of 304 and 440C stainless steel.

Element	304 (% Content)	440C (% Content)
Fe	68.6	79.15
Cr	19	17
Ni	9.25	0
C	0.08	1.1
Mn	2	1
Si	1	1
Mo	0	0.75
P	0.045	0
S	0.030	0



Scheme 2. Effects of different (304 vs. 440C S.S.) metal vials.

Table 4. Reduction of benzaldehyde promoted by a single metal.[a]



1g 2g

Entry	Metal	% Conversion[b]
1	Al	65
2	Mn	71
3	Zn	84
4	Cr	53
5	Fe	3
6	Ni	99
7	Mo	7
8	Cu	0
9	Ag	0

[a] Conditions 0.6 mmol of 1 g, 30 mmol water, 18 mmol metal, and 5 PTFE balls [b] Percentage calculated based on ^{1}H NMR integrations.

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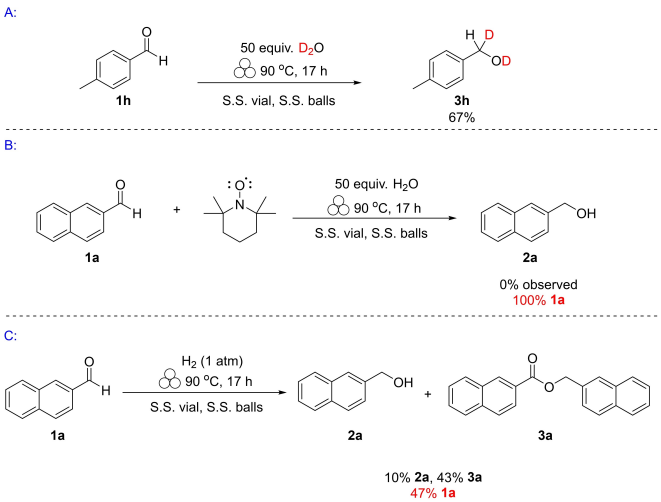


Scheme 3. Experiments for the mechanistic investigation: (A) D_2O was used instead of H_2O to confirm the source of hydrogen. (B) A Radical scavenger, TEMPO, was added to the reaction to determine the likelihood of a SET mechanism. (C) Molecular hydrogen was added to reaction in absence of water to determine if water is required in the hydrogenation stage.

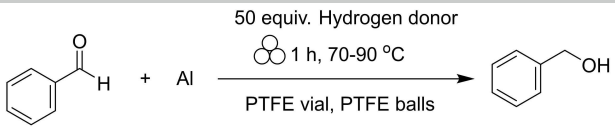
found that the methylene position had 67% deuteration, confirming that the hydrogen from water is incorporated into the organic product. To confirm SET as part of the mechanism, a radical scavenger, (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO), was used in an equimolar ratio to **1a** to intercept a potential radical intermediate. There was no evidence of **2a** being formed under the conditions that would typically yield **2a** quantitatively. Finally, water was excluded from the reaction and 1 atm of dihydrogen was introduced to determine if dihydrogen formation preceded the reduction. Dihydrogen was introduced to the reaction by setting up the reaction vial inside of a small glove bag that was evacuated and subsequently filled with H_2. A small amount of **2a** was observed, with the major component of the reaction mixture being the starting material **1a**. However, another large component of the reaction mixture (43%) was identified as 2-naphthylmethyl 2-naphthoate (**3a**). The presence of this product provides evidence supporting that even under dihydrogen, the conversion of aldehyde to alcohol requires a proton source or higher pressure of dihydrogen. Without either of these factors, the radical anion resulting from the reduction of **1a** may transfer a hydride to another molecule of **1a**, mimicking a Tishchenko-type reaction. This type of hydride transfer from a radical anion intermediate has been shown to produce benzyl benzoate from benzaldehyde in nonpolar solvents, which would be comparable to the conditions during this mechanochemical reaction.[25] The hydrogen that is necessary to produce the alcohol may be from the adventitious water present in **1a**. Though the vial and balls were dried thoroughly prior to the reaction, the starting material was not.

Further investigation was carried out to determine whether the reaction takes place by SET between a single metal and water to generate dihydrogen followed by a hydrogenation process, or through direct SET between the metal and the organic substrate followed by protonation of the organic substrate. Here, a study using different sources of hydrogen with a reactive metal was conducted for the reduction of benzaldehyde (**1g**). According to the metal reactivity series, reactive metals such as sodium, potassium, and lithium are not safe to operate under the reaction conditions. To avoid any safety concerns, aluminum was selected as the reactive metal. Isopropanol and ethanol were chosen as the hydrogen donors, and the temperatures employed were elevated but not high enough to vaporize them. The results show that only a trace amount of **1g** was reduced (Table 5). Although using aluminum in the presence of water as the hydrogen source resulted in a moderate conversion for **1g**, (entry 3), using aluminum with ethanol and isopropanol (entries 1 and 2, respectively) under similar conditions resulted in almost no conversion for **1g**. The inductive effect of the alkyl group in the alcohols must slow down the reactivity of the alcohols with aluminum. The results here appear to support that SET occurs between aluminum and water. The alternative mechanism involving SET between aluminum and the organic substrate followed by protonation can be ruled out.

To shed additional light on the mechanistic sequence of SET followed by hydrogenation, two ketone substrates (**1l** and **1m**) were chosen to be reduced with Fe pellets and $NiCl_2$. A catalytic amount (10 mol%) of $NiCl_2$, and a greatly reduced amount of water was chosen for the reaction because of the results from a measurement to record the mass loss of stainless steel. During the naphthaldehyde optimization studies, it was found that the stainless-steel vial lost 30 mg and the stainless-steel balls lost 9.5 mg. This mass loss indicates a substoichiometric amount of stainless steel potentially used in the reaction, indicating the metals may be catalytic for this process. As shown in Scheme 4, even with just 1.5 equiv of water, **1l** and **1m** were reduced to the corresponding alcohols **2l** and **1n**. This result suggests that iron is integral for the SET step, and it is possible that nickel may be needed for the hydrogenation step of this reduction process.

The involvement of a SET mechanism in the carbonyl reduction reaction prompted us to hypothesize that the stainless steel may act like an electrochemical cell in a mechanochemical system. The implications of performing electrochemical experiments mechanochemically could be

Table 5. Reduction experiments using alternative hydrogen donors.[a]



1g 2g

Entry	Hydrogen donor	Temperature [°C]	% Conversion[b]
1	Ethanol	70	0
2	Isopropanol	75	0
3	Water	90	65

[a] Conditions: 0.6 mmol substrate, 18 mmol aluminum, 50 equiv alcohol and 5 PTFE balls. [b] Percentage calculated based on ^{1}H NMR integrations.

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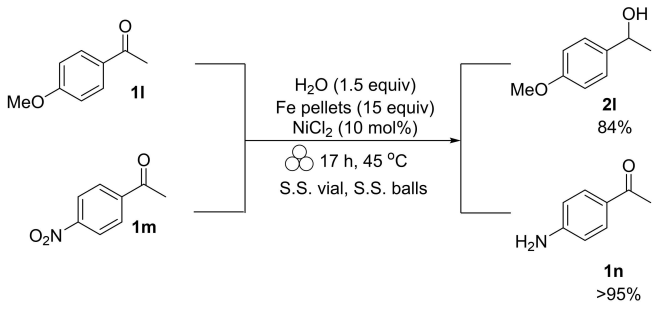


Scheme 4. Reduction of substrates facilitated by $NiCl_2$.

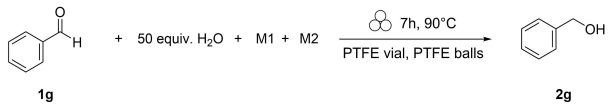
significant. Recent studies have demonstrated using various recyclable piezoelectric materials to carry out mechanoredox reactions.[26,27] Using recyclable piezoelectric materials for electro mechanochemical reactions has shown a significant potential for developing more sustainable and efficient chemical synthesis methods.[28,29] Organic electrochemistry is a relatively new, simple, and environmentally benign methodology.[30] However, the method has intrinsic challenges that hinder its full adoption as a tool for organic synthesis. For example, diffusion limitations for the organic substrate to the electrode surface are difficult to overcome, and proper solvent choice to dissolve both organic substrate and the electrolyte is challenging.[31,32] Using piezoelectric materials mechanochemical to drive electrochemical reactions has encouraged us to explore ways to perform mechanoelectrochemical reactions.

To test this hypothesis, studies with mixed metals were then performed to test metal combination cell potential in the ball mill system. Like in Table 4, the experiments were conducted in a PTFE-lined vial with PTFE balls to eliminate the effect of the metals within the stainless-steel vial and the stainless-steel balls. The PTFE vial was loaded with different metal combinations of Ni, Cr, Fe powders with >99% purity. The cell potentials were calculated based on the reported standard reduction potentials of the metals.[33] Initially, the reduction of benzaldehyde (1 g) was examined with Fe/Ni, Fe/Cr and Cr/Ni combinations (Table 6). These results show that using Fe/Ni and Fe/Cr combinations led to a quantitative conversion (entries 1 and 2), while using Cr/Ni led to a moderate conversion (entry 3).

Next, acetophenone (**1o**) was used as a representative ketone substrate to further understand the effect of mixed metals (Table 7). The reaction with the Fe/Ni combination resulted in a high conversion (entry 1). On the other hand, the use of Fe/Cr and Cr/Ni diminished the conversion (entries 2 and 3). The presence of chromium metal appears to have suppressed the reduction of acetophenone. These results do not show enough of a difference between the Fe/Cr and Cr/Ni combinations to determine if this also follows the expected trend of the cell potential. It is possible that the exact cell potential is difficult to predict by calculation because of comproportionation of the metals. That is, the calculated potentials assume a metal oxidation state of zero. While on average the metal oxidation states may be zero in the physical system, it does not necessarily mean that each atom has an oxidation state of zero at any given time.

To study the chemoselectivity of aldehydes over ketones, an equimolar amount of benzaldehyde and acetophenone was subject to reduction using the same metal combinations (Table 8). The Fe/Ni combination was shown to be nonselective, as it reduced both substrates with high conversions (entry 1). However, the Fe/Cr and Cr/Ni combinations did demonstrate some selectivity. Both combinations (entries 2 and 3) resulted in a preferential reduction of **1g** to **2g**, although the Cr/Ni combination displayed a slower reaction rate. These results imply that the Fe/Ni combination is the most reactive out of the ones tested. Furthermore, these results suggest that adjusting the cell potential by changing the metals may result in chemoselective reactions, which opens the door for mechanochemistry to enter the field of organic electrochemistry.

Table 6. Reduction of benzaldehyde with mixed metals.[a]

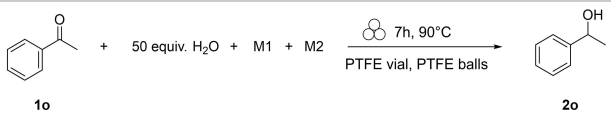


1g 2g

Entry	M1	M2	% Conversion[b]	Cell potential
1	Fe	Ni	>99	0.19
2	Fe	Cr	>99	0.30
3	Cr	Ni	48	0.49

[a] Conditions [a]0.6 mmol of substrate, 30 equiv. of M1 and M2, 50 equiv. water and 5 PTFE balls [b] Percentage calculated based on ^{1}H NMR integrations.

Table 7. Reduction of acetophenone with mixed metals.[a]

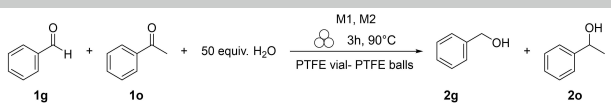


1o 2o

Entry	M1	M2	% Conversion[b]	Cell potential
1	Fe	Ni	70	0.19
2	Fe	Cr	Trace	0.30
3	Cr	Ni	Trace	0.49

[a] Conditions [a]0.6 mmol of substrate, 30 equiv. of M1 and M2, 50 equiv. water and 5 PTFE balls [b] Percentage calculated based on ^{1}H NMR integrations.

Table 8. Chemoselectivity for reduction with mixed metals.[a]



1g 1o 2g 2o

Entry	M1	M2	% **1g**[b]	% **1o**[b]	Cell potential
1	Fe	Ni	>99	90	0.19
2	Fe	Cr	>99	Trace	0.30
3	Cr	Ni	45	Trace	0.49

[a] Conditions [a]0.6 mmol of substrate, 30 equiv. of M1 and M2, 50 equiv. water and 5 PTFE balls [b] Percentage calculated based on ^{1}H NMR integrations.

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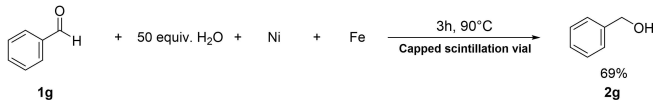

Scheme 5. Scintillation vial control reaction.

Though PTFE is a lighter material than stainless-steel, the authors are still confident that mechanochemistry is still necessary to obtain the conversions reported for the mixed-metal studies. A control reaction in a scintillation vial was performed for the reduction of benzaldehyde (Scheme 5). Under mechanochemical conditions, the same reaction resulted in quantitative conversion, where a temperature-controlled water bath resulted in 69% conversion. It is not surprising that this moderate conversion was obtained since metal powders were being used (as opposed to raw metal that is not already pulverized). However, the markedly lower conversion does indicate that mechanochemistry is still required to obtain similar results.

Conclusion

This work demonstrates the importance of understanding and controlling temperature for the reduction of aldehydes and ketones with metal and water. The ability to control the temperature of this reaction provides the opportunity to understand the reaction mechanisms in greater detail. Under the conditions tested, iron is the most reactive reductant, and different substrates require different temperatures for reduction. Most substrates undergo reduction at 45 °C, but for the less reactive ones, increasing the temperature appears to drive the reaction to completion more quickly. Further mechanistic studies indicate that the mechanism by which the carbonyl and other unsaturated bonds are reduced is through single electron transfer (SET). Finally, the results for the reduction reactions using mixed metals indicate that mechanochemistry may be a system in which organic electrochemistry can occur, possibly avoiding the problems associated with electrochemistry like solubility of electrolyte and substrate. Further experiments are currently underway to apply this strategy to other electrochemical reactions.

Experimental Section

General remarks: Reactions were carried out by mechanochemical milling in a SPEX8000M Mixer Mill at a frequency of 18 Hz using a stainless-steel vial with seven 440C stainless-steel balls (size 3/16"), unless otherwise noted. ^{1}H and ^{13}C $\{^{1}H\}$ NMR spectra were obtained on a Bruker Avance 400 MHz spectrometer, and all chemical shift values are reported in ppm on the δ scale. GC-MS data were obtained from a Hewlett-Packard 6890 series GC-MS with a Zebron ZB-5, 15 mm × 0.25 mm × 0.25 mm column. Normal-phase TLC was performed using silica gel plates purchased from Silicycle and analyzed by UV light. Flash column chromatography was performed using a Combiflash® Automated Flash Column Chromatography system with RediSep Rf Gold® high performance flash columns (fine spherical silica gel 20–40 μm). Deuterated chloroform was obtained from Cambridge Isotope Laboratories, Inc., Andover, MA, and used without further purification. All aldehydes and ketones were purchased from Sigma Aldrich or Acros Organics. Most were used without further purification. Benzaldehyde was purified by vacuum distillation prior to use. All 304 stainless-steel reaction vials were custom made at the University of Cincinnati machine shop and the metal rods were purchased from McMaster Carr®. The reaction used to test 440C stainless steel used a 15-mL stainless steel SmartSnap™ grinding jar from Form-Tech Scientific. The stainless-steel balls were also purchased from McMaster Carr®. Simiriz 486 Perfluoroelastomer O-rings (6/16" ID × 7/16" OD × 3/32" width) were purchased from Small Parts Inc. and used to prevent leaking with custom made vials.

Typical procedure for reduction reaction: To a custom-made 2.0 × 0.5-inch stainless steel screw capped vial was added seven 440C stainless steel balls (size 3/16"). 2-naphthaldehyde (1.21 mmol, 189 mg) was added to the vial. Via a pipet, 50 equiv of water (0.060 mol, 1.09 g) was added to the vial. To the cap, a perfluoroelastomer O-ring was inserted. The vial and cap were screwed together using a vice and wrench and placed in a Spex Certiprep 8000M mixer mill. For heated reactions in Figure 1, the vial was placed in the heating apparatus and then in a Spex Certiprep 8000M mixer mill. An "iButton" (DS1922E, Maxim Integrated Circuits, http://www.ibutton.com) was clamped between the top of the jar and the clamp assembly to measure the temperature throughout the reaction. All other heated reactions were set up using a PID-heater controller, as described in the report by Andersen and Starbuck.[34] The reagents were milled for 17 h. After milling, the reaction mixture was extracted with acetone and transferred to an Erlenmeyer flask. The Erlenmeyer flask was then decanted over a funnel fitted with fluted filter paper into a pre-weighed round bottom flask. The solvent was removed under reduced pressure to afford the products.

Reduction with mixed metals: To a PTFE SmartSnapTM grinding jar was added seven PTFE ball (size 3/16"). Substrate (0.60 mmol) was added to the vial, followed by the addition of metal powders (30 equiv each). Via a pipet, 50 equiv of water (30 mmol, 0.54 g) was added to the vial. The vial is placed in a Spex Certiprep 8000M mixer mill. For heated reactions, the vial was placed in the heating apparatus and then in a Spex Certiprep 8000M mixer mill. The reagents were milled for a desired period of time. After milling, the reaction mixture was extracted with ethyl acetate and transferred to an Erlenmeyer flask. The Erlenmeyer flask was then decanted over a funnel fitted with fluted filter paper into a pre-weighed round bottom flask. The solvent was removed under reduced pressure to afford the products. ^{1}H NMR and GC-MS were used to assess the purity of the alcohol products. All alcohol products were characterized with ^{1}H NMR spectroscopy and found to agree with the literature data. The characterization data are also listed below. Purified product spectra can be found in the Supporting Information.

Scintillation vial control reaction: To a 20-mL scintillation vial, benzaldehyde (0.60 mmol, 63.60 mg) was added followed by the addition of Fe and Ni powders (30 equiv each). Via pipet, 50 equiv of water (30 mmol, 0.54 g) was added to the vial. The scintillation vial was capped and placed in a temperature-controlled water bath at 90 °C for 3 h. After the reaction was complete, the mixture was extracted with ethyl acetate and transferred to an Erlenmeyer flask. The flask was decanted over fluted filter paper into a round bottom flask where the solvent was then removed under reduced pressure to afford a mixture of benzaldehyde and benzyl alcohol. ^{1}H NMR and GC-MS were used to assess the purity of the benzyl alcohol.

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: carbonyl group · mechanochemistry · oxidizable metals · reduction · temperature-controlled milling

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