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Quantifying zinc and manganese reduction potentials in organic solvents

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Zinc and manganese are the reductants of choice for nickel-catalyzed cross-electrophile coupling (XEC), but their exact redox potentials are unknown in organic solvents. In a recent report from Stahl and colleagues in *Nature Chemistry*, these potentials have been measured for the first time and their implications on model XEC reactions have been discussed.

Ni-catalyzed XEC reactions have emerged as a powerful strategy for the construction of C–C bonds from a feedstock of readily available electrophiles (Figure 1A, i).[1] This approach bypasses the need for organometallic nucleophilic coupling partners. These reductive couplings need a supply of electrons to generate a low-valent Ni species that engages organic halides via oxidative addition or halogen-atom abstraction reactions. The most commonly used reductants are zinc (Zn) or manganese (Mn) metal powders in the zero-valent state, due to their ease of handling.[2] Alternatives include organic amines[3] and electrochemical methods,[4] which allow homogeneous reaction conditions and tunable reduction potentials, respectively. The commonly cited two-electron reduction potentials for Zn and Mn are often based on simple mathematical conversion of the aqueous reduction potentials (versus the standard hydrogen electrode) to the relevant reference electrode in non-aqueous solvents. While this approach can be employed in reaction optimization based on trial and error reasonably well, it is an oversimplification of the complex non-aqueous medium in which XEC reactions are usually performed (Figure 1A, ii). This is evident in the electrochemically irreversible cyclic voltammograms (CVs) of $ZnBr_2$ and $MnBr_2$ in acetonitrile or DMF, suggesting sluggish electron transfer kinetics.

In order to reliably measure the $Zn^{2+/0}$ and $Mn^{2+/0}$ reduction potentials, the authors make use of a simple and powerful electrochemical technique of open circuit potential (OCP) measurement.[5] OCP experiments performed over time measure the thermodynamic potential of a redox pair without current flow. This means that the reduction potentials can be measured without any perturbation from electrochemical kinetics. The authors make use of a standard three-electrode setup, where the working electrode is the metal of interest, the counter electrode is a platinum coil, and the reference electrode is a standard non-aqueous $Ag/AgNO_3$ electrode (Figure 1A, iii). It is important to note that during OCP measurements, the potentiostat effectively functions as a voltmeter, measuring the potential difference between the working and the reference electrodes. The analyte solution used was a 10 mM dibromide salt of the same metal, which simplifies the Nernst equation of the $M^{2+/0}$ pair such that the formal potential measured is offset from the thermodynamic potential by 59 millivolts (mV). With this methodology, the authors report OCP measurements of Zn, Mn, and other metal reductants in several solvents and with additives that are commonly used in XEC reactions.

In general, the authors found that Zn^0 was less reducing than Mn^0 with an average value of approximately −1.3 V for $Zn^{2+/0}$ and −1.5 V for $Mn^{2+/0}$ versus the ferrocene/ferrocenium ($Fc^{+/0}$) redox couple (Figure 1A, iv). An interesting lowering of potential was observed in acetonitrile (−1.07 V for $Zn^{2+/0}$ and −1.19 V for $Mn^{2+/0}$), presumably due to the formation of solvated metal salts. As a comparison, a simple conversion of the reported aqueous reduction potentials to $Fc^{+/0}$ in MeCN yields potentials of −1.4 V for $Zn^{2+/0}$ and −1.8 V for $Mn^{2+/0}$. The observed anodic shift of the reduction potentials in MeCN was then used to rationalize an observation made by Weix and colleagues[6] for the Ni-catalyzed XEC of benzyl chloride with phenyl iodide (Figure 1B, i). The reaction in the original report employed Zn as a reductant and proceeded smoothly in dimethylacetamide (DMA) but furnished **1** in MeCN in 15% yield. Making use of the newly measured potentials in an electrochemical reaction, the authors show that the reduction potential dictates the yield of the product. Low amounts of product were formed at an applied potential of −1.07 V, while high yields were obtained at −1.35 V (the measured E^0 for $Zn^{2+/0}$ in DMA) in both DMA and MeCN. The effect of additives commonly used in XEC reactions was also analyzed. A particularly intriguing observation was the marked cathodic shift of the reduction potentials of both Zn and Mn when halide salts were added in various solvents, explaining the beneficial role of common

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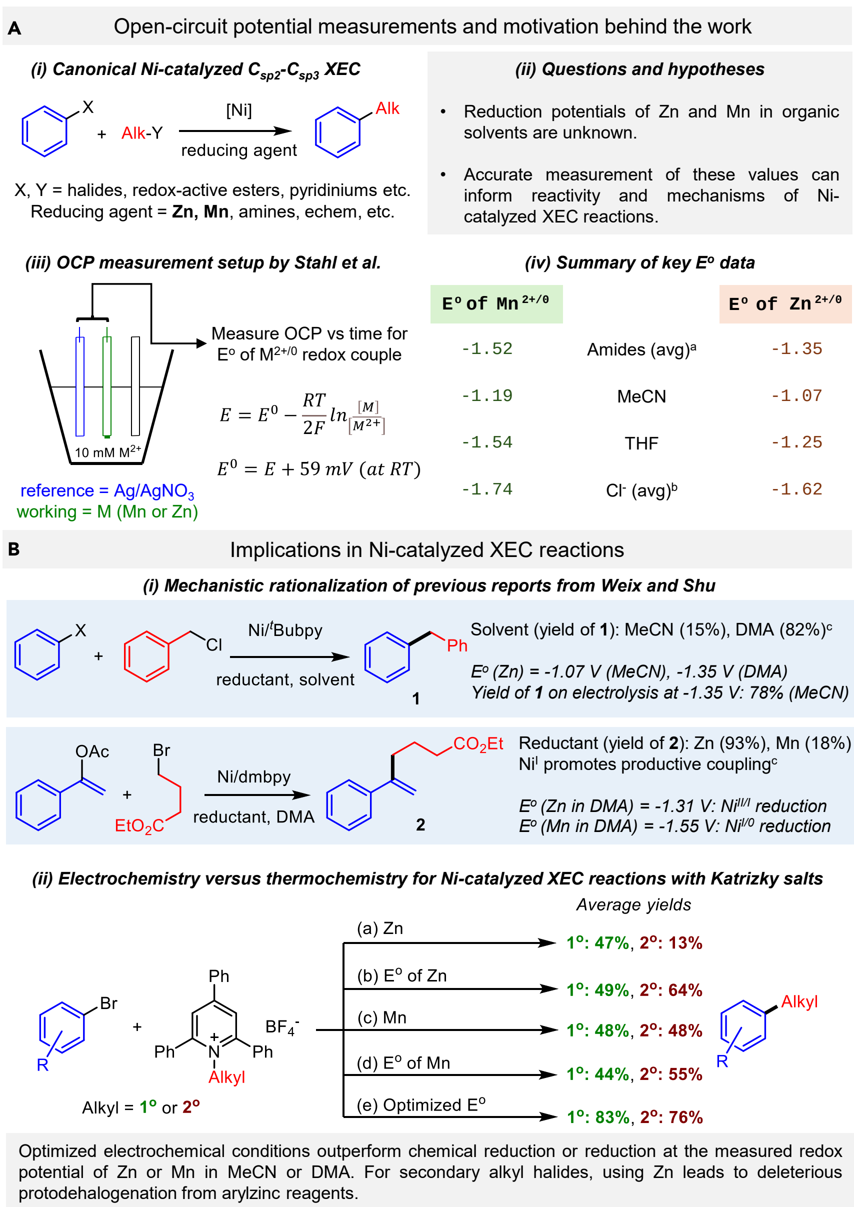

Figure 1. Measurement of Zn and Mn reduction potentials and their implications in nickel-catalyzed XEC reactions

(A) Background on Ni-catalyzed XEC, open circuit potentials, and some of the key Zn and Mn redox potential data reported in the study by Stahl and colleagues.[10]

(B) (i) Applications of redox potential data in understanding the mechanisms of previously reported XEC reactions. (ii) Comparison of the performance of thermochemical versus electrochemical XEC reactions.

[a]Amide solvents include DMF, DMA, NMP (N-methylpyrrolidine), DMPU (N,N′-dimethylpropyleneurea), and DMI (1,3-dimethyl-2-imidazolidinone).

[b]Solvents in which chloride salts were tested as additives include MeCN, THF, and DMF.

[c]Experimental results presented in previous studies.

The text in italics represents the data presented in the study by Stahl et al. dtbpy = 4,4′-di-*tert*-butyl-2,2′-dipyridyl; dmbpy = 4,4′-dimethyl-2,2′-bipyridine.

additives like lithium chloride (LiCl). The authors also uncovered a concentration dependence for LiCl on the Zn reduction potential in DMF, with higher LiCl concentrations making Zn more reducing.

With the insights gained from the large library of reduction potentials in various solvents, the authors then undertook an electroanalytical investigation of two Ni-catalyzed XEC reactions reported by Shu and colleagues[7,8] The cross-coupling of alkenyl acetates and alkyl bromides was found to proceed with Zn as the reductant (Figure 1B, i), but not with Mn. The opposite preference was observed for the XEC between oxalic esters and aryl triflates. For the first reaction, CV experiments revealed that the $Ni^{II/I}$ reduction to generate the proposed active Ni^I-alkenyl species was accessed at a potential suited for Zn. The authors argue that the reduction potential of Mn is ideally suited to reduce Ni to its zero-valent state, which promotes deleterious side reactions like homocoupling. For the second reaction, the key oxidative addition of the inert aryl triflate occurs at a more reduced Ni^0 and catalytic currents were observed at potentials more reducing than −1.6 V. This observation led the authors to conclude that the less reducing Zn was ill suited to generate such low-valent Ni species, leading to the observed selectivity. Electrochemical analysis to investigate the role of these heterogeneous reductants in XEC is a powerful approach to provide support for mechanistic claims, and we anticipate this approach will be widely adopted by the community.

The authors conclude the study with a set of experiments that directly compare thermochemical and electrochemical catalysis for a set of XEC reactions between (hetero)aryl bromides and alkyl Katrizky salts.[9] Five sets of experiments (two chemical and three thermochemical, Figure 1B, ii) were performed for each reaction by varying the source of electrons: (a) Zn, (b) electroreduction at E° of Zn in the solvent, (c) Mn, (d) electroreduction at E° of Mn in the solvent, and (e) electroreduction at an optimized E° for the given reaction. For the first set of reactions with primary alkyl Katrizky salts, the yields for the thermochemical (a and c) and electrochemical experiments (b and d) for Mn and Zn correlated well. For the second set of reactions with secondary alkyl Katrizky salts, the use of Zn as a reductant was deleterious due to the formation of the organozinc reagents from the aryl bromides which were rapidly protodehalogenated. Catalysis at the optimized electrochemical potential (e), which was often performed at a potential different from the Mn or Zn potentials, outperformed the first four conditions for both reactions. The authors also show that electrolysis at the optimized potential was successful for a few reactions where neither chemical reductant could furnish synthetically useful yields of the cross-coupled product. This highlights the power of modulating the potentials by electrochemistry, even though a drawback of this approach is the necessity of optimizing the applied potential by performing several experiments for each reaction. However, using electrochemistry to perform XEC does offer a significant advantage in scaling up these reactions in which the use of heterogeneous reductants poses several operational challenges. A complementary approach to electrochemistry for scaling up is the use of soluble organic bases like tetrakis(dimethylamino)ethylene (TDAE), which obviates issues caused by mass transfer.[3]

In summary, the work by Stahl and colleagues utilizes OCP measurement as a tool for measuring the true thermodynamic potentials of two of the most commonly used reductants in organic chemistry.[10] This fills an important knowledge gap, as commonly quoted potentials for heterogeneous reductants in organic chemistry rarely consider the complexities of the nonaqueous solvent systems in which these reactions take place. In addition, having well-defined reduction potentials for these inexpensive reductants in organic solvents will also serve as an invaluable tool for organometallic synthesis. The authors went on to examine the role of Zn and Mn as reductants in the context of Ni-catalyzed XEC. Important insights into the thermodynamic influence of various additives were obtained and mechanistic rationale for previous observations in catalytic systems could now be provided with these reduction potential values in hand. The authors conclude the study by highlighting the benefits that bulk electrolysis can offer over employing chemical reductants for a few model XEC reactions. However, the operational simplicity of using metal powders as reductants would still make them the reagents of choice for many laboratories,[2] and this work provides important guidelines to rationally make such choices.

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DECLARATION OF INTERESTS

The authors declare no competing interests.

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