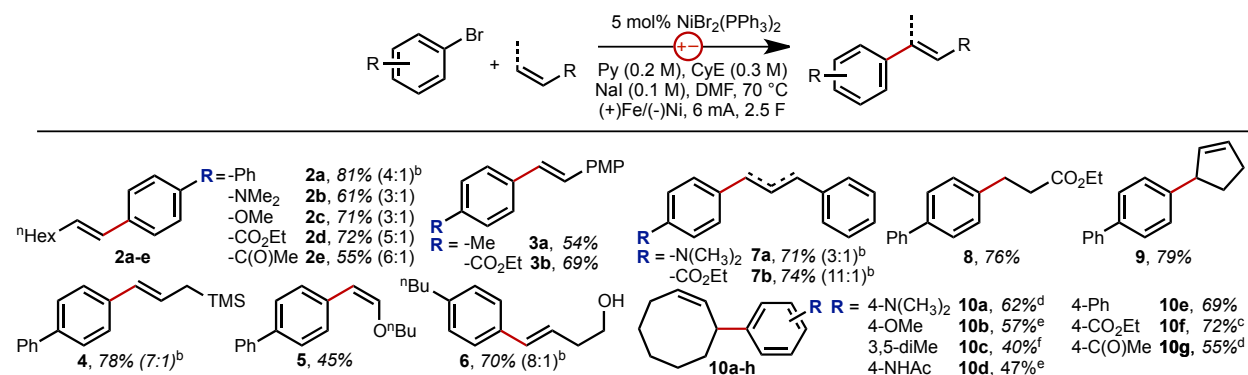
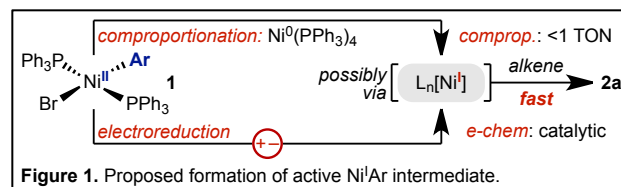


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2. Project Title: *Electrically-Driven, Catalytic C-C Bond-Forming Reactions: Strategies, Methods, and Mechanisms*
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**Alkene Functionalization:** Despite parallels in reactivity between Ni and Pd complexes, Ni-catalyzed Heck reactions of aryl halides are very rare. This inability to use an inexpensive metal in place of Pd is particularly problematic for industries that specialize in the synthesis of commodity or agrochemicals because the final products must be inexpensive to the consumer. Developing inexpensive systems that catalyze Heck coupling will allow scientists to directly utilize abundant petrochemical feedstocks such as alkenes and aryl electrophiles.

In this budget period, we discovered rare examples of Ni-catalyzed Heck couplings of aryl bromides with both activated and unactivated alkenes under mild conditions. The hypothesis-driven approach to the development of these reactions relied on mechanistic data that implicated low-valent analogs of Ni(aryl) complexes as key intermediates. Unlike Pd-catalyzed Heck reactions, Ni(II)aryl complexes alone are kinetically incompetent for Heck coupling. Rather, product formation required the formation of a transient Ni(I) intermediate.

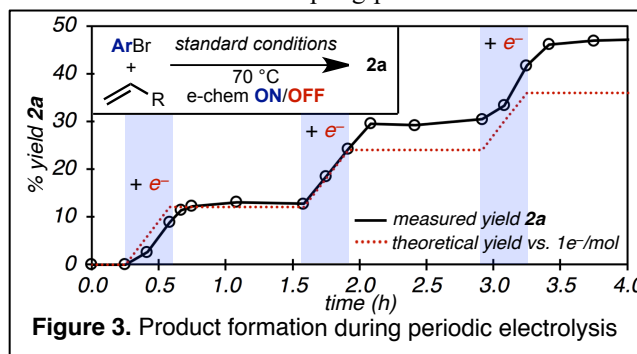
Our approach to rendering this challenging reaction catalytic was to utilize electrochemistry as a means for reduction of the Ni(II)aryl complex. While electrochemistry can easily access the reducing potentials of Ni(0), phosphine-ligated complexes of Ni generally have ill-defined redox events at potentials that allow competitive protodehalo-



**Figure 2.** Scope of electrochemically-promoted Heck coupling.

genation of the aryl halides. To address this critical limitation, we discovered that electrolysis could be conducted with electron deficient olefins (cyclohexenone) as additives to promote reduction of the Ni(II)aryl complex in preference to the aryl bromide, and thus mitigate protodehalogenation. Importantly, coupling was observed exclusively with the unactivated substrate in preference to the cyclohexenone additive. With these conditions in hand, we demonstrated the application of electrochemical activation of inexpensive Ni complexes to catalyze the Heck coupling of a range of substrates (Figure 2). As a result, this work represents an electrochemical activation of an unreactive first-row metal complex to mimic the high catalytic activity of precious-metal analogs.

Finally, detailed mechanistic studies suggest that the electrochemical Heck coupling proceeds via an electron-chain transfer process with multiple products formed from each transferred electron. This catalytic utilization of electrons indicates that Ni-catalyzed Heck coupling *does not* require stoichiometric reduction, as would be expected if electroreduction served only to assist with turnover of a Ni(hydride) intermediate. Rather, these studies suggest that the reaction is net redox-neutral and that relies on electroreductive activation of a Ni(II)aryl intermediate. Overall these insights underscore the use of electrochemistry as an effective means for activation of inexpensive, but unreactive, complexes to catalyze desirable transformations.



**Phosphine Reduction:** While evaluating various ligands for the electrochemical Heck reaction, we discovered that electrolysis of solutions containing triphenyl phosphine oxide (TPPO) as a potential ligand resulted in almost exclusive formation of triphenyl phosphine (TPP). Selective reduction of TPPO to TPP under mild conditions has been long sought after because of the massive scale on which TPPO is generated in the synthesis of petrochemical analogs (alkenes). Current approaches for TPPO reduction require multistep syntheses or strong reductants at high temperatures. Our strategy utilizes an Al anode as an inexpensive electron source that generates  $\text{Al}^{3+}$  upon oxidation. In the presence of a ligand, the  $\text{Al}^{3+}$  serves as an effective Lewis acid for the activation of TPPO and reductive P–O bond cleavage. Our discoveries represent the first example of room-temperature reduction of TPPO on multigram scale at high concentration (0.5 M) and in high yields (>85%). We anticipate the simplicity of this approach will be attractive to industrial process groups, and this work highlights the impact that electrochemistry can have on the petrochemical industry.

**Catalyst Overcharge Protection:** Our final research effort targeted the development of electroreductive cross-electrophile coupling reactions for a range of alkyl substrates that are challenging under conventional conditions: secondary substrates. We quickly discovered that catalytic intermediates are susceptible to overreduction, which result in catalyst degradation and formation of undesired side products. The seemingly-simple coupling of an aryl bromide and cyclohexyl bromide results in low yields of coupled material and high yields of protodehalogenation. To address this, we employed soluble battery materials that could reversibly accept electrons and prevent overreduction of the catalyst. These battery materials were selected such that they have redox potentials that are above that which is required for degradation, but lower than that which is required for catalysis (Figure 4).

Coupling reactions conducted with battery materials at tuned redox potentials provided coupled products in high yields with a broad range of substrates. In contrast, identical reactions in the absence of the battery material generated products in only 5-30% yield (see reactions for **8c**, **15a**, **15d**, **16**). Overall these findings represent new strategies for utilizing shuttles in synthetic electrochemistry that will further support the establishment of our long-term research program.

