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# An Electrochemically-Promoted, Nickel-Catalyzed, Mizoroki-Heck Reaction

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ABSTRACT: Despite significant efforts to replace Pd-based catalysts with those of Ni, the Ni-catalyzed Mizoroki-Heck coupling of aryl halides and alkenes remains challenging. This work details the development of a Mizoroki-Heck reaction of aryl halides and a broad range of alkenes that utilizes electrochemistry as a means to promote Ni-catalyzed coupling under mild conditions. Stoichiometric studies implicate low-valent Ni complexes as key intermediates in route to rapid reactions with even unactivated alkenes. As such, electrochemistry is employed to readily provide the reducing potentials necessary to access these reactive intermediates and render the transformation catalytic. Cyclohexenone was found to be an unreactive substrate, but a crucial additive that promotes facile electroreduction of the nickel catalyst and functionalization of other alkenes in high yields. Finally, preliminary mechanistic studies suggest that reactions proceed via an electron-chain transfer process that rapidly terminates but is reinitiated upon electroreduction. **KEYWORDS:** electrochemistry, Heck reaction, alkene functionalization, cyclic voltammetry, redox, catalysis

#### INTRODUCTION

Metal-catalyzed C–C bond-forming reactions have revolutionized retrosynthetic approaches to organic synthesis.<sup>1,2</sup> Among these transformations, the Mizoroki-Heck coupling of alkenes and aryl electrophiles to form vinyl arenes has been implemented in both commodity and fine-chemical processes.<sup>3–8</sup> While Heck coupling has historically relied on Pd-based catalysts,<sup>9–11</sup> recent efforts have been aimed at designing Ni analogs as inexpensive catalysts for this transformation.<sup>12–14</sup> The evolution of important methodologies to systems that employ catalysts of earth-abundant metals has been realized for an extensive number of C–C<sup>15–24</sup> and C–N<sup>25–28</sup> bond-forming reactions that were once known only for Pd and are now readily catalyzed by Ni complexes with similar – or greater – rates and turnover numbers.<sup>13</sup>

Despite parallels in reactivity between Ni and Pd complexes, Ni-catalyzed Heck reactions of aryl halides remain rare. Such reactions with even the most activated alkenes require forcing conditions (>130 °C) and high metal/ligand loadings (>15 mol%), often negating the cost-benefit of Ni.<sup>20,29–33</sup> Recently, Ni-catalyzed Heck reactions have been found to proceed under mild conditions when conducted with aryl sulfonates or with added sulfonylating reagents.<sup>29,34–36</sup> This strategy exploits the facile ionization of Ni-sulfonates to form cationic Ni-hydride intermediates that are more acidic and more readily deprotonated for catalyst turnover than a neutral Ni(hydrido)halide.

While these transformations are restricted to systems that access cationic intermediates, they highlight the dramatic influence of charge at the metal on reactivity. Similarly, conditions for Pd-catalyzed Heck coupling have been developed with the aim of accessing anionic or cationic intermediates that are more reactive than their neutral analogs.<sup>8,10,37–39</sup> Adding to these strategies, *this work reveals the influence of electron transfer on the rate of Ni-catalyzed Heck reactions*. Specifically, we report the

utilization of electrochemistry to promote a rare example of Nicatalyzed Heck coupling between aryl halides and a broad range of activated and unactivated alkenes under mild conditions. Key to the development of this reaction is the addition of cyclohexenone, which itself does not undergo coupling, but was found to promote reduction of Ni intermediates and coupling of other alkenes. Finally, preliminary studies suggest that the Heck coupling proceeds via an electron-chain transfer process that rapidly terminates but is reinitiated under electroreductive conditions.



**Figure 1.** (a) Observations from stoichiometric reactions. (b) Hypothesis and approach to Ni-catalyzed protocols.

## **RESULTS AND DISCUSSION**

Although uncommon, Heck reactions have been conducted under reductive conditions,<sup>40,41</sup> but are limited to reactions of activated alkenes, such as styrene,<sup>42,43</sup> acrylates,<sup>44–46</sup> or ethylene,<sup>45</sup> and provide few mechanistic insights to guide development of a general process. Moreover, reactions commonly suffer from extensive dimerization of the aryl halide and competitive overreduction. This promising, but poorly-understood, area was of particular interest to our program that focuses on accelerating metal-catalyzed reactions with electrochemistry. We first evaluated reactions of Ni(II)aryl complexes (1) that are generally unreactive towards alkenes. As expected, stoichiometric reactions of 1 with excess 1-octene formed low yields of Heck-coupled products (24% vs. Ni) over the course of 12 h at 70 °C (Figure 1a, top). However, directly subjecting a combination of aryl bromide, 1-octene, and Ni<sup>0</sup>(PPh<sub>3</sub>)<sub>4</sub> to 70 °C formed Heck products in 60% yield within just 30 minutes (Figure 1a, bottom). No additional product was formed in the subsequent 2 h at 70 °C. Analysis of mixtures that result from stoichiometric reactions with *para*-fluoro-bromobenzene by <sup>19</sup>F NMR spectroscopy indicated that the resting states of Ni during this dormant period is the Ni(II)aryl analog of 1.

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These data led us to hypothesize that unlike Pd-catalyzed Heck reactions,<sup>10,39</sup> the Ni(II)aryl complex (1) alone is kinetically incompetent for Heck coupling. Rather, product formation requires a combination of both 1 and a low-valent Ni species. Nickel complexes are well-known to undergo comproportionation,<sup>47,48</sup> and this electron-transfer process is possible at the onset of reactions containing Ni<sup>0</sup>(PPh<sub>3</sub>)<sub>4</sub> (Figure 1b). Following oxidative addition, remaining Ni(0) can serve as a reductant to enable turnover of Ni(hydride) intermediates, or to form a low-valent Ni(aryl) complex that reacts rapidly with alkenes. Migratory insertion at Ni(I) centers has been recently implicated as an elementary step in Ni-catalyzed alkene functionalization<sup>49-51</sup> or haloarene carboxylation.<sup>52,53</sup> However, Ni(0) eventually forms the thermodynamically-preferred complex 1, as detected by NMR spectroscopy, and can no longer serve as a reductant to promote Heck coupling. This process suppresses catalysis as yields are limited to less than one turnover of nickel. Nonetheless, these insights suggest that sustained reduction of 1 would enable Heck couplings of arvl bromides that are (i) catalyzed by inexpensive complexes of Ni, (ii) rapid under mild conditions, and (iii) compatible with a broad scope of alkenes.



Figure 2. Electroreduction in the presence of additives. Yields are calculated by GC analysis based on complex 1. Reactions were conducted with 0.250 mmol ArBr, 1.25 mmol 1-octene, 0.038 mmol 1, and 0.038 mmol  $e^{-}$  (1 $e^{-}$  vs. Ni). PyCN = 4-cyanopyridine, BTD = benzothiadiazole, MMI = *N*-methyl methylisonicotinate iodide, dba = dibenzylideneacetone, CyE = cyclohexenone.

Our approach to rendering this challenging reaction catalytic was to utilize electrochemistry as a means for reduction of **1**. 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 competetive protodehalogenation of the aryl halides (*vide infra*; < -2 V vs. Ag/Ag<sup>+</sup>).<sup>54,55</sup> As evidence, 1e<sup>-</sup> reduction of **1** in the presence of excess 1-octene and biphenylbromide primarily results in dehalogenation, but does form Heck products in 39% yield vs. Ni (Figure 2).

To promote reduction of 1 in preference to the aryl bromide, and thus mitigate protodehalogenation, we performed electrolysis with additives that could (i) transiently generate a redox-active Ni(II)aryl intermediate by ligation (PyCN, BTD), (ii) serve as a redox mediator (BTD, MMI), or (iii) stabilize low-valent nickel intermediates (dba, chalcone, CyE).<sup>56–59</sup> These experiments revealed that addition of electron-deficient alkenes dramatically improved reaction yields over those of direct electrolysis of **1**. In particular, 1e<sup>-</sup> electrolysis of the iso-lated Ni(aryl) complex in the presence of excess aryl bromide and cyclohexenone (CyE) as an additive formed Heck products in 115% yield, demonstrating catalytic turnover. In addition, coupling was observed exclusively with the unactivated alkene in preference to CyE, which is a common substrate for Heck coupling with Pd as catalyst.<sup>60,61</sup>

These insights guided development of a catalytic methodology using biphenylbromide and 1-octene as model substrates (Table 1). Competing protodehalogenation to form biphenyl could be easily monitored by gas chromatography, and catalysts that successfully couple these unbiased substrates would likely be reactive towards more activated alkenes. Ultimately, constant-current electrolysis of an inexpensive catalyst system, based on the combination of NiBr<sub>2</sub>•3H<sub>2</sub>O and triphenylphosphine (PPh<sub>3</sub>), in an undivided cell with a Ni cathode and Fe anode led to >95% yields of Heck products and less than 2% protodehalogenation (entry 1).

#### Table 1. Reaction Development<sup>a</sup>

Ph 1 equ	+ nHex Br iv 7 equiv	10 mo 5 mol% M pyridine cyclohexe Nal (0.1 M) (+)Fe/(-)Ni	I% PPh <sub>3</sub> ViBr <sub>2</sub> •3H <sub>2</sub> O (2 equiv) none (0.3 M) 0, DMF, 70 °C , 6 mA, 2.5 F	Ar 2a + branched isomer
entry	deviation from st	andard	% conversion	% yield (I:b)
1	none		100	>95 (4:1)
2	no electrochemistr	'y	<5	0
3	no NiBr <sub>2</sub> •3H <sub>2</sub> O		15	0
4	no cyclohexenone		99	21
5	no PPh <sub>3</sub>		100	29
6	Zn anode		59	9
7	2.5 equiv Zn <sup>0</sup> powder as reductant		ctant 35	31
8	no pyridine		98	57
9	Et <sub>3</sub> N instead of pyridine		100	55
10	25 mol% pyridine		100	88
11	2,2'-bipyridine inst	ead of PPh3	97	23
12	dppe instead of PI	Ph <sub>3</sub>	45	41 (1:1)
13	Ph <sub>2</sub> P(2-pyridyl)		99	>95

<sup>a</sup>GC yields of combined linear and branched isomers. dppe = 1,2bis(diphenylphosphino)ethane.

Control experiments demonstrate that electrochemistry, nickel, CyE, and phosphine are all crucial for high yields (entries 2-5). Reactions performed with a Zn anode in place of Fe suffered from surface passivation of the anode and required cell potentials of >2 V to maintain the applied current (see the SI, Figure S3). The catalyst is likely incompatible with the high cell voltage, as reactions resulted in incomplete conversion and low yields (9%, entry 6). Efforts to promote the reaction with an excess of Zn<sup>0</sup> powder as a chemical reductant in place of electroreduction similarly resulted in low yields (31%, entry 7). The choice of pyridine as base was particularly important for reactions that afford products in high yields. Heck couplings require base to both promote catalyst regeneration and sequester acidic byproducts. Thus, the low yields obtained from reactions without pyridine were expected (entry 8). However, reactions conducted with a variety of other bases, including Et<sub>3</sub>N (entry 9), resulted in yields that were nearly identical to those of reactions lacking base altogether. While these non-pyridyl bases had no 1

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effect on the reaction outcome, the addition of just 25 mol% pyridine to reaction mixtures afforded products in 88% yield (entry 10). The positive effect of even substoichiometric quantities of pyridine on the reaction led us to evaluate pyridyl complexes of Ni as catalyst. However, reactions conducted with chelating tri- and bipyridines led to low yields (entry 11). Other chelating ligands, including bisphosphines, similarly formed inactive catalysts for Heck coupling (entry 12). Despite the possibility for chelation, reactions with (2-pyridyl)diphenylphosphine generated products in excellent yields that are comparable to those of reactions with inexpensive PPh<sub>3</sub> (entry 13).

Finally, reactions of the model substrates provided insights into the selectivity for linear versus branched products. With the exception of entry 12, linear products were formed in preference to branched products with a ratio of 4:1 from all reactions in Table 1, as well as from the stoichiometric reactions illustrated in Figure 1. The similarities in product selectivity from reactions with and without PPh<sub>3</sub> (entry 1 vs. entry 5) suggest that C-C bond formation is mediated by an organometallic intermediate that lacks a bound phosphine. Similar linear-tobranched ratios of 4:1 have been observed from alkene arylation reactions with "ligandless" Pd complexes, which further supports the intermediacy of a phosphine-free complex under the electrochemical conditions.<sup>10,62,63</sup> In contrast, Heck coupling catalyzed by cationic Ni intermediates predominantly forms branched products.<sup>29,64</sup> The complementary selectivities of these Ni-catalyzed methodologies can be attributed to the distinct strategies in reaction design. These data represent a rare example of Ni-catalyzed Heck coupling that directly replicates the reactivity and selectivity observed from catalysts of Pd.



**Chart 1. Substrate Scope.** Yields shown are isolated yields from reactions of 0.3 mmol of ArX. <sup>a</sup>Ratio of linear to branched products. <sup>b</sup>9 mA at 100 °C. <sup>c</sup>9 mA at 70 °C. <sup>d</sup>9 mA at 85 °C. <sup>e</sup>3 mA at 70 °C.<sup>f</sup>97% GC yield from iodide. <sup>g</sup>70% isolated yield from 1.05 g reaction. <sup>h</sup>3 mA with 150 mM alkene. PMP = *para*-methoxyphenyl. Tol = *para*-tolyl

With these conditions in hand, we explored the scope of the electrochemically-promoted reaction. Reactions of 1-octene with a variety of aryl bromides or iodides generate Heck products in just over 3 h that can be isolated in good yields (Chart 1). Linear products were formed in preference to branched products, and highest linear selectivities were observed from reactions with the most electron-deficient aryl halides (2e vs 2b). Reactions of polarized alkenes were found to generate only linear products. Styrenyl substrates readily undergo coupling to generate stilbenes (3a-b) with some diminished yield due to oligomerization. Finally, these electrochemical conditions were readily scaled without additional optimization to generate 2a in 70% yield on a gram scale.

Not limited to just activated alkenes, we evaluated reactions of a range of aliphatic alkenes. Surprisingly, high selectivities for linear products were observed from reactions of alkenes that had just minor steric or electronic perturbations of the  $\pi$  system. As examples, reactions of allyl tetramethylsilanes (4), vinyl ethers (5), homoallylic alcohols (6), and homoallylic sulfones (11) form coupled products in excellent yields, from which linear products can be isolated in good yields. The linear vinyl ethers formed from this electrochemical methodology complement the branched products that are prone to hydrolysis to acyl arenes and formed by previously-reported systems.<sup>29</sup> Finally, the high yield of 6 highlights tolerance of free alcohols under the electroreductive conditions and that chain walking to form aldehydic products is slow.<sup>65–67</sup>

This lack of olefin isomerization led us to probe the selectivity of B-hydride elimination by studying reactions of allylbenzene. Carbonickelation of allylbenzene with varying aryl substrates would form Ni(alkyl) intermediates that can undergo βhydride elimination at two benzylic positions. Hydrogen atoms at these positions are likely distinguishable only by the electronic effects imparted by the adjacent aryl groups. Palladium analogs of such pseudo-symmetric intermediates have been shown to undergo elimination with the most hydridic H atom, which is at the benzylic position of the most electron-donating aryl fragment.<sup>68</sup> Reactions under our electrochemical conditions generated ratios of isomers that are nearly identical to those generated by Pd catalysts. Product 7a was formed with a 2.1:1 preference for elimination toward the electron-donating (dimethylamino)phenyl group, while 7b was formed with a 1.1:1 preference for elimination away from the electron-withdrawing aryl group. These product mixtures likely represent catalyst selectivity, rather than a thermodynamic ratio of products from isomerization, because other kinetic isomers have been observed under the reaction conditions. Specifically, significant amounts of unconjugated, allylic products were generated in reactions that form 2a-2e, and product 5 was formed in a 4:1 ratio favoring the Z over E isomer.

In addition to terminal alkenes, cyclic substrates are reactive under the developed conditions (9, 10a-g). A range of electrophilic, acidic, and basic functional groups are tolerated to form allylic products. Formation of these products supports a mechanism that involves syn carbonickelation across the alkene, followed by elimination of the only syn-coplanar  $\beta$ -hydrogen. The mild conditions employed for the generation of allylic products contrast the conditions required for conventional Ni-catalyzed Heck couplings (150 °C), which generate vinylic products exclusively.<sup>33</sup>

Finally, ethyl acrylate is reactive under the conditions, but reactions yield only alkyl products from a formal reductive-Heck process (8). While acrylates are common substrates for Pd-catalyzed Heck reactions,<sup>31,32</sup> this result indicates that further reduction outcompetes  $\beta$ -hydride elimination of the Ni(alkyl) intermediate. Despite this reactivity with ethyl acrylate, the cyclic analog and key additive, CyE, does not undergo competitive coupling with the aryl halides and only 5-15% is lost over the course of the reaction.

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We investigated the role of CyE by comparing electrode potentials during electrolysis to potentials of redox events identified by cyclic voltammetry (CV). Measurements against a Ag/Ag<sup>+</sup> quasi-reference electrode during the course of the reaction revealed an anodic potential of -0.4 V (Figure 3a, blue trace) and a cathodic potential of -1.5 V (red trace). These potentials are consistent with the cell voltage of ~1.1 V that is commonly observed for reactions. The anodic potential at -0.4 can be ascribed to oxidation of the sacrificial Fe anode,<sup>69</sup> but reduction at -1.5 V was not of the Ni(II)aryl complex 1 alone (Figure 3b, black trace). Scanning to increasingly negative potentials of a reaction mixture containing 1 in the absence of CyE revealed no well-defined reduction of the complex. Rather, the observed current at an onset of -2.1 V is that of haloarene reduction. In contrast, CV of the same solution after addition of CyE revealed a reduction event with an onset potential of -1.5 V (red trace). This reduction event has a potential that matches that of the cathode during electrolysis and is exclusively observed when both 1 and CyE are present in solution. CyE alone undergoes reduction at the more negative potential of -2.2 V (blue trace). These data implicate a stabilizing interaction between the electron deficient additive and the reduced nickel intermediate to allow reactions to be conducted at mild potentials that preclude degradation of the aryl bromide.



**Figure 3.** a) Voltaic profiles of the anode (blue) and cathode (red) for the standard reaction. b) CVs of complex **1** and CyE at 70 °C (return sweeps were omitted for clarity).

Finally, we monitored product formation during the course of a reaction that was periodically electrolyzed to gain insight into the Faradaic efficiency (Figure 4). As expected, the NiBr<sub>2</sub> precursor was inactive without electrochemistry. Application of a constant current generated a non-linear yield-response that is consistent with consumption of electrons for precatalyst activation. Despite this nonproductive initial use of electrons, 1.05 equivalents of product had been formed for every e- passed. Subsequent electrolysis periods further highlight the high efficiency of e<sup>-</sup> utilization, both generating 1.33 equivalents of product for every e<sup>-</sup> passed. 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 data, and those of Figure 3, are more consistent with a reaction that is net redox-neutral and that relies on electroreductive activation of a Ni(II)aryl intermediate.



Figure 4. Product formation during periodic electrolysis.

The short period of product formation following electrolysis further supports this hypothesis. Once electrolysis ends, the Ni(0) generated from catalyst turnover can continue to facilitate the reaction as a homogeneous reductant. This radical-chain process eventually terminates when Ni(0) undergoes oxidative addition of an aryl bromide to form of an unreactive Ni(II)aryl complex. Reactivation of this complex requires an exogenous reductant. Overall these insights underscore the use of electrochemistry as an effective means for activation of inexpensive, but unreactive, complexes to catalyze desirable transformations.

#### CONCLUSION

In summary, we report rare examples of Ni-catalyzed Heck couplings of aryl bromides with both activated and unactivated alkenes under mild conditions. The hypothesis-driven approach to reaction development relied on mechanistic data that implicate low-valent analogs of Ni(aryl) complexes in Heck coupling reactions. We demonstrate that electrochemistry is a facile means for accessing the low potentials required for reduction of the unreactive Ni(II) complexes. As a result, this work represents an electrochemical activation of an unreactive first-row metal complex to mimic the high catalytic activity of preciousmetal analogs. Detailed mechanistic studies to identify reactive intermediates and develop processes for substoichiometric reduction are ongoing.

#### ASSOCIATED CONTENT

#### **Supporting Information**

Experimental procedures, cell design, characterization of compounds, spectroscopic data, electrochemical data, and additional experiments are supplied. This material is available free of charge via the Internet at http://pubs.acs.org.

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## ACKNOWLEDGMENT

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