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Electrochemically Assisted Heck Reactions

Jun Tian and Kevin D. Moeller*

Department of Chemistry, Washington University, St. Louis, Missouri 63130

moeller@wustl.edu

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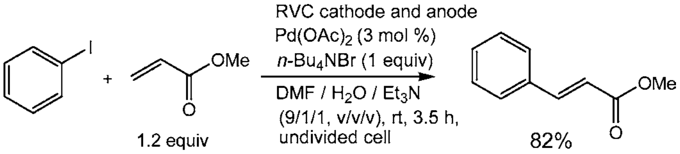
ABSTRACT



During efforts to develop chip-based Heck reaction chemistry, it was discovered that normal solution-phase Heck reactions can be dramatically accelerated using electrochemistry. The acceleration makes room temperature Heck reactions proceed at synthetically useful rates in the absence of added ligand. Presumably, the current passed through the reaction maintains a high level of active catalyst.

Recently, we reported the development of a site-selective Heck reaction on an electrochemically addressable, semiconducting chip.[1] In this work, pre-selected electrodes on the chip were used to reduce $Pd(OAc)_2$ and generate the required Pd(0) catalyst. The Pd(0) catalyst was then confined to the region of the chip surrounding the selected electrode by adding allyl methyl carbonate to the reaction. The allyl methyl carbonate scavenged the Pd(0) catalyst by converting it into an inactive π-allylpalladium(II) species. As with any such reaction, optimization of spatial selectivity on the chips benefited from reaction conditions that showed only a minimal amount of background reaction in the absence of an active electrode. For the Heck reaction, this was accomplished by running the reactions at room temperature in the absence of phosphine,[2] thiourea,[3] or carbene[4] ligands.[5] For example, a reaction between methyl 4-iodobenzoate and 1-pyrenemethyl acrylate took 18 h to reach completion when treated with $Pd(OAc)_2$ in a 9:1 DMF/water solution containing triethylamine and tetrabutylammonium bromide.[6] The reaction did not proceed at all when the DMF solvent was exchanged for acetonitrile. The reaction proceeded in 3 and 12 h, respectively, when a cathode was inserted into the reaction, and the $Pd(OAc)_2$ reduced electrochemically. This observation made it clear that site-selective, chip-based Heck reactions were possible. It also suggested that preparative-scale, room-temperature Heck reactions might benefit from the passage of current. A similar observation was made by Mangold and Jüttner in their work utilizing polypyrrole/palladium composite modified cathodes.[7] Using this heterogeneous catalyst and "electrochemically-driven" conditions, the authors found that the Heck coupling of iodobenzene to styrene could be accomplished at room temperature without additives. However, the yield of stilbene product obtained was very low (5×10^{-5} M product for a reaction using 0.1 M substrate). Our work in connection with chip-based reactions indicated that this would not be the case for Heck reactions involving a homogeneous catalyst. We report here conditions for electrochemically assisted Heck reactions that not only significantly accelerate the room-temperature Heck

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[1] Tian, J.; Maurer, K.; Tesfu, E.; Moeller, K. D. *J. Am. Chem. Soc.* **2005**, *127*, 1392.

[2] For room-temperature Heck reactions in the presence of phosphine ligands, see: (a) DeVasher, R. B.; Moore, L. R.; Shaughnessy, K. H. *J. Org. Chem.* **2004**, *69*, 7919. (b) Stambuli, J. P.; Stauffer, S. R.; Shaughnessy, K. H.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 2677. (c) Littke, A. F.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 6989. (d) Hiroshige, M.; Huaske, J. R.; Zhou, P. *Tetrahedron Lett.* **1995**, *36*, 4567. (e) Jeffery, T. *Tetrahedron Lett.* **1994**, *35*, 3051.

[3] For a room-temperature Heck reaction using a thiourea-based ligand, see: Dai, M.; Liang, B.; Wang, C.; Chen, J.; Yang, Z. *Org. Lett.* **2004**, *6*, 221.

[4] For a room-temperature Heck reaction using a carbene-type ligand, see: Andrus, M. B.; Song, C.; Zhang, J. *Org. Lett.* **2002**, *4*, 2079.

[5] For Heck reactions accelerated using ultrasound, see: (a) Ambulgekar, G. V.; Bhanage, B. M.; Samant, S. D. *Tetrahedron Lett.* **2005**, *46*, 2483. (b) Deshmukh, R. R.; Rajagopal, R.; Srinivasan, K. V. *Chem. Commun.* **2001**, *33*, 1544.

[6] A prior room-temperature Heck reaction using $Pd(OAc)_2$ and related conditions showed similar results: Jeffery, T. *Tetrahedron Lett.* **1985**, *26*, 2667.

[7] Mangold, K.-M.; Meik, F.; Jüttner, K. *Synth. Met.* **2004**, *144*, 221.

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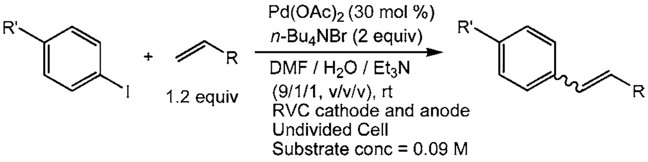
reactions in the absence of added ligands but also lead to excellent yields of product.

Our study of these reactions began by examining the generality of the electrolysis conditions developed for the chip-based reactions. This was accomplished by coupling iodobenzene to a series of electron-poor, electron-rich, and conjugated olefins (Table 1). The electrolysis reactions utilized 15 mA of current, reticulated vitreous carbon (RVC) anodes and cathodes, and an undivided cell. In each case, passing current through the cell led to more than a 4.5-fold increase in the rate of the Heck reaction. In the best case (entry 8a vs entry 8b), a 9-fold increase in rate was observed. The rate acceleration was not changed by the presence of an electron-withdrawing group on the aryliodide (entry 7−9) or the use of a platinum cathode.

Table 1. Use of Aryliodide Substrates



entry[a]	R′	R	time (h)	electricity (F/mol)	yield (%) (*trans/cis*)
1a	H	CO_2Me	16	none	85 (*trans* only)
1b	H	CO_2Me	2.5	1.22	89 (*trans* only)
2a	H	Ph	18	none	84 (*trans* only)
2b	H	Ph	4	1.33	87 (*trans* only)
3a	H	$CONH_2$	16	none	81 (*trans* only)
3b	H	$CONH_2$	3	1.57	84 (*trans* only)
4a	H	n-$C_8H_{16}CO_2Me$	18	none	74 (4.2/1)
4b	H	n-$C_8H_{16}CO_2Me$	3.5	1.47	84 (4.2/1)
5a	H	CN	16	none	80 (3.4/1)
5b	H	CN	2.5	1.37	82 (3.4/1)
6a	H	OEt	12	none	70 (4.6/1)
6b	H	OEt	2	1.06	78 (4.6/1)
7a	CO_2Me	CO_2CH_2-pyrene	18	none	78 (12/1)
7b	CO_2Me	CO_2CH_2-pyrene	4	1.78	84 (12/1)
8a	CO_2Me	$CONH_2$	18	none	80 (*trans* only)
8b	CO_2Me	$CONH_2$	2	0.91	85 (*trans* only)
9a	CO_2Me	Ph	18	none	80 (*trans* only)
9b	CO_2Me	Ph	3	1.26	88 (*trans* only)

[a] a = no current; b = 15 mA.

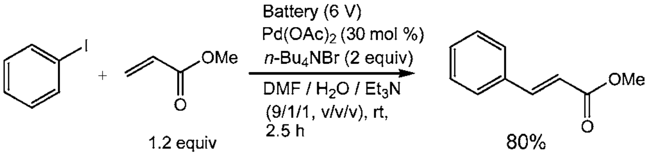
When the reaction utilized in entry 7b was performed using a platinum cathode, the reaction proceeded in 3 h and generated an 82% isolated yield of product. In each example studied, the yield for the electrochemically assisted reaction was slightly higher than the yield for the nonelectrochemical reaction. The product stereochemistry obtained from the reactions was the same for both electrochemical and non-electrochemical reactions.

The increased reaction rate required passing current through the cell for the entire duration of the experiment. When current was passed for 1 h through a cell containing the substrates for reaction 7b and then stopped, the Heck reaction took 14 h to reach completion. The reaction was 20% complete when the current was turned off. Clearly, when the current was stopped the reaction returned to being a normal room-temperature, ligand-free Heck reaction. This behavior suggests that the rate acceleration is not simply due to a very efficient initial reduction of Pd(II) to the active Pd(0) catalyst. Instead, it appears that the current passed continually maintains a higher level of active catalyst than found in the absence of current. At this time, the exact role of the current in the reactions is not known. However, it is thought that the concentration of active catalyst in ligand-free Heck reactions is reduced by the aggregation of unstable Pd(0) clusters to form catalytically inactive precipitates.[8] One plausible explanation for the role of the current in the reactions is that the clusters being formed are broken up by the oxidation of Pd(0) to Pd(II) at the anode (the reactions are run in an undivided cell).[9] Rereduction of the Pd(II) species at the cathode then effectively recycles the palladium back into catalytically active Pd(0) species. The net result is a steady state of active catalyst.

From a practical standpoint, the compatibility of the reactions with the redox cycle and the presence of a steady-state concentration of Pd(0) is very important because it allows for the use of a simple constant current reaction setup. In a constant current reduction, the potential of the cathode climbs after the electrolysis substrate is consumed, a development that can lead to the reduction of electron-poor products and a decrease in product yield. However, in the case of the redox cycle described above, the reaction never runs out of Pd(II) substrate and the potential at the cathode remains constant for the entire duration of the experiment. Hence, there is no risk of reducing the Heck reaction product and no need to regulate the potential at the cathode.

The ability to run the reactions using constant current conditions means that the experiments are compatible with the use of a readily available 6-V lantern battery as the power supply (Scheme 1).[10,11] Although the use of a battery does lead to a lower yield of product (compare with Table 1, entry 1b), the success of the reaction makes it clear that the utility

Scheme 1



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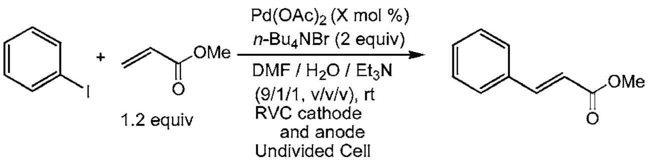
[8] Reetz, M. R.; de Vries, J. G. *Chem. Commun.* **2004**, *35*, 1559

[9] **Sample Experimental Procedure.** To a 25 mL three-neck flask with a mixture of iodobenzene (2.45 g, 12.0 mmol), methyl acrylate (1.25 g, 14.4 mmol), $Pd(OAc)_2$ (80.8 mg, 0.36 mmol), and tetrabutylammonium bromide (3.86 g, 12.0 mmol) was added a solution of 9 mL of DMF, 1 mL of water, and 1 mL of triethylamine. The resulting brown solution was electrolyzed with constant current (15.0 mA) on reticulate vitreous carbon (RVC) electrodes at room temperature under an argon atmosphere until iodobenzene was consumed (3.5 h). HCl (1 M) was then added to the reaction mixture until a pH <5 was reached. The resulting suspension was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were first washed with water and brine and then poured into a short pad column with silica gel eluting with CH_2Cl_2. The CH_2Cl_2 elute was concentrated under reduced pressure. The residue was chromatographed on silica gel eluting with hexane/ethyl acetate (15/1) to afford (*E*)-methylcinnamate (1.60 g) in 82% yield.

of the method with new substrates can be readily evaluated without the need for specialized equipment.

After establishing that the effect of the electrolysis on the Heck reaction was general, we turned our attention to finding the optimal catalytic conditions. In other words, do the reactions really require 30 mol % of the catalyst? The results of these studies are summarized in Table 2. When the amount of catalyst was decreased (entry 3), the rate of the reaction initially dropped. A 3-fold reduction in catalyst led to a 2-fold drop in rate. The reaction rate could be restored by increasing the current flow through the cell from 15 mA to 25 mA (entry 4). However, the increase in current lowered the yield of the reaction. Fortunately, the rate of the reaction could also be restored by increasing substrate concentration (entry 5). With this in mind, the concentration was raised further (entry 6), and *the reaction proved compatible with the use of only 3 mol % catalyst*. Optimal conditions for the reaction used a substrate concentration equal to 0.88 M (entry 7).

Table 2. Optimizing Catalytic Activity

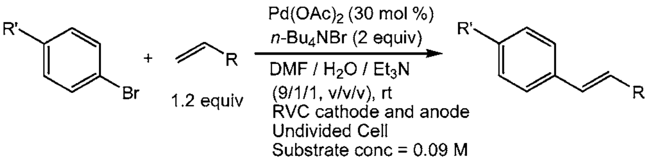


entry	X (mol %)	time (h)	substrate conc (M)	current (mA)	electricity (F/mol)	yield (%)
1	30	16	0.09	none	none	85
2	30	2.5	0.09	15	1.22	89
3	10	5	0.09	15	2.86	85
4	10	2	0.09	25	2.05	76
5	10	2	0.27	15	1.12	85
6	3	4.5	0.49	15	2.94	80
7^a	3	3.5	0.88	15	2.05	82

^{a} This reaction used 1 equiv of electrolyte.

The passage of current through reactions utilizing less reactive arylbromide substrates also led to significant improvements in both the rate of the reactions and the yield of product obtained (Table 3). Since the reactivity of the arylbromides is very low, the reactions were explored using 30 mol % of the catalyst. With these conditions, a room-temperature Heck reaction between bromobenzene and styrene produced little product even after 18 h (entry 1a). On the other hand, the electrochemically assisted reaction afforded a 62% isolated yield of product (entry 1b). Similar results were obtained when electron-withdrawing groups were added to either the arylbromide or the olefin substrate. Unlike the aryliodide-derived reactions, the arylbromide-derived reactions were not compatible with the use of electron-rich olefin coupling partners.

Table 3. Use of Arylbromide Substrates



entry^a	R′	R	time (h)	electricity (F/mol)	yield (%)
1a	H	Ph	18	none	<10
1b	H	Ph	6	3.19	62
2a	CO$_2$Et	Ph	18	none	32
2b	CO$_2$Et	Ph	6	3.34	74
3a	CO$_2$Et	CONH$_2$	20	none	0
3b	CO$_2$Et	CONH$_2$	5.5	3.15	58
4a	NO$_2$	Ph	20	none	78
4b	NO$_2$	Ph	5	2.84	80
5a	NO$_2$	CO$_2$Me	24	none	72
5b	NO$_2$	CO$_2$Me	5.5	3.13	75

^{a} a = no current; b = 15 mA.

Along similar lines, room-temperature Heck reactions using aryl chloride substrates could not be successfully completed.

In conclusion, we have found that room-temperature Heck reactions can be enhanced without the addition of a ligand by passing current through the reaction. The current leads to a significant increase in reaction rate and improved yields. It appears that the enhancement of the reactions is the result of the electrolysis maintaining a high level of active catalyst. The reactions can be performed using a very simple reaction setup by taking advantage of a battery as the power supply. Finally, it is interesting to consider what the success of these reactions suggests about electrochemically accelerating other organometallic reactions.[12]

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Supporting Information Available: Sample procedures and spectral data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) For a simple electrochemical setup using a battery as a power supply, see: Frey, D. A.; Wu, N.; Moeller, K. D. *Tetrahedron Lett.* **1996**, *37*, 8317.

(11) All "non-battery" experiments were conducted using a model 630 coulometer, a model 410 potentiostatic controller, and a model 420A power supply purchased from The Electrosynthesis Co., Inc. This equipment is now available from Electrolytica, Inc.

(12) For an application of electrochemistry to a tin-based allylsilane reaction, see: Zha, A.; Hui, A.; Zhou, Y.; Miao, Q.; Wang, Z.; Zhang, H. *Org. Lett.* **2005**, *7*, 1903.