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A Highly Selective and General Palladium Catalyst for the Oxidative Heck Reaction of Electronically Nonbiased Olefins

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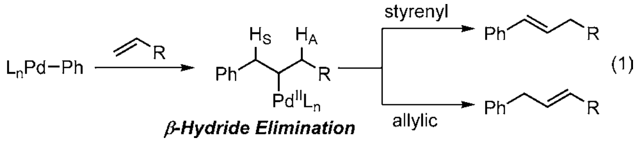
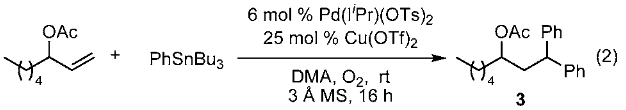
Abstract: A general, highly selective oxidative Heck reaction is reported. The reaction is high-yielding under mild conditions without the need for base or high temperatures, and the selectivity is excellent, without the requirement for electronically biased olefins or other specific directing groups. A preliminary mechanistic investigation suggests that the unusually high selectivity may be due to the catalyst's sensitivity to C−H bond strength in the selectivity-determining β-hydride elimination step.

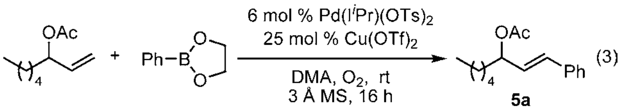
The oxidative Heck reaction, a transformation in which a vinylic C−H bond is converted to a C−C bond under $\mathrm{Pd^{II}}$ catalysis, has the potential for broad synthetic applications.[1,2] Unfortunately, most examples require the use of an electronically biased olefin such as an acrylate to deliver high selectivity for the (*E*)-styrenyl product. A notable exception recently reported by White and co-workers[3] is proposed to rely on substrate chelation to afford these products as the only observable isomer. The poor selectivity under typical Heck conditions presumably arises from the metal center's lack of ability to distinguish between H_S or H_A when undergoing β-hydride elimination (eq 1), resulting in a mixture of often-inseparable styrenyl and allylic products.[4] Herein, we report a highly selective and general oxidative Heck reaction with a unique preference for the (*E*)-styrenyl products governed by catalyst control. Additionally, this reaction does not require base and is efficient at mild temperatures.



We recently reported an olefin diarylation reaction that utilizes the oxidative Heck mechanistic manifold but intercepts reactive $\mathrm{Pd^{II}}$−alkyl intermediates with an arylstannane in a second transmetalation event (eq 2).[5] The success of this system was partially attributed to the cationic nature of the catalyst. In view of the ubiquitous nature of arylboronic acid derivatives in cross-coupling, we chose to evaluate these in our alkene difunctionalization reactions. To our surprise, the use of phenylboronic ester **4a** in place of $\mathrm{PhSnBu_3}$ afforded only the (*E*)-styrenyl Heck product **5a** with no observed diarylation or isomeric products (eq 3).

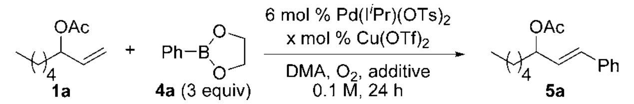


1a **2** (3 equiv) **3** 68% yield



1a **4a** (3 equiv) **5a** 23% yield

Table 1. Optimization of the Oxidative Heck Reaction



entry	additive	temperature	*x*	% conversion[a]	% yield[a]
1	3 Å MS	rt	25	22	19
2	3 Å MS	40 °C	25	>99	85
3	−	40 °C	25	98	93
4	−	40 °C	20	>99	>99
5[b]	−	40 °C	20	<1	<1
6	−	40 °C	0	64	12
7[c]	−	40 °C	20	5	5

[a] Conversion and yield were calculated by comparing starting material and product peak integrations to the integration for an internal standard using GC analysis. [b] No $\mathrm{Pd(I^iPr)(OTs)_2}$ was used. [c] The reaction was run under nitrogen.

Optimization of this reaction was performed, and it was found that raising the temperature to 40 °C improved the yield without diminishing the selectivity. Removing molecular sieves (MS) and decreasing the $\mathrm{Cu(OTf)_2}$ loading further improved the GC yield to >99% with >20:1 selectivity for the (*E*)-styrenyl isomer (Table 1). Finally, performing the reaction in the absence of the $\mathrm{Pd^{II}}$ catalyst, $\mathrm{Cu(OTf)_2}$, or O_2 resulted in little to no reactivity (entries 5−7). Submission of substrate **1a**, which is susceptible to β-acetoxy elimination, to the optimized reaction conditions on a 0.5 mmol scale resulted in a 95% yield of the desired product (Table 2, entry 1).[6]

In view of the unusually high selectivity observed, we chose to examine the scope of this transformation. The reaction proved to be tolerant of a wide variety of functional groups commonly encountered in organic synthesis, delivering the desired (*E*)-styrenyl product in a >20:1 ratio in most cases. Electron-deficient arylboronic esters were highly effective (Table 2, entries 2 and 3). A substrate containing a TBS-protected homoallylic alcohol gave good yields and high selectivity for a range of arylboronic esters (entries 4−7). A free homoallylic alcohol was also a compatible substrate, delivering the desired product in moderate yield (entry 8). Other functional groups on simple alkenes were well-tolerated, including a distal free alcohol (entry 9), a primary chloride (entry 10), a ketone (entry 11), and an ester (entry 12). Use of a hindered arylboronic ester required increased catalyst loading and elevated temperatures, resulting in a reduction in selectivity (10:1 olefin isomer ratio; entry 13). An acetonide-protected diol was an excellent substrate even though a Lewis acidic catalyst was used (entry 14). Nitrogen-containing substrates are incompatible with previously reported reactions utilizing this catalyst, but an allylic amine with two carbamate protecting groups (entry 15) performed well in the present reaction. However, a more electron-rich carbamate led to poor catalyst activity (entry 16). Finally, a substrate containing a trisubstituted olefin (entry 17), which may preferentially bind to but not react with the catalyst, was a poor substrate under these

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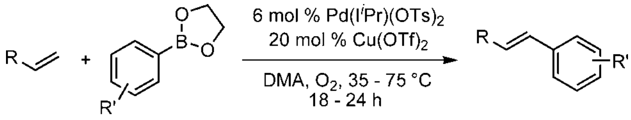
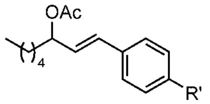
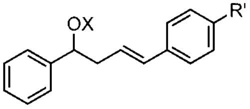
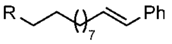
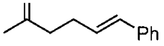
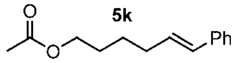
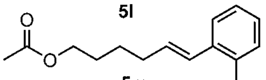
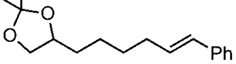
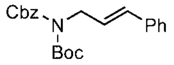
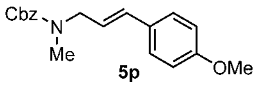
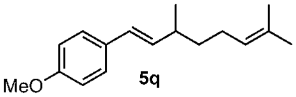
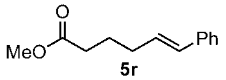
Table 2. Scope of the Oxidative Heck Reaction

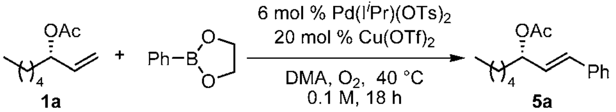


1 **4** (3 equiv) **5**

entry	product	temperature	% yield^a
1	**5a**	40	95
			
2	R' = C(O)OMe **5b**	45	97
3	R' = CF_3 **5c**	45	73
			
4	X = TBS, R' = H **5d**	35	81
5	X = TBS, R' = OMe **5e**	35	80
6	X = TBS, R' = F **5f**	45	87
7	X = TBS, R' = C(O)Me **5g**	45	78
8	X = H, R' = H **5h**	40	63^b
			
9	R = OH **5i**	35	80^b
10	R = Cl **5j**	35	89^b
11	 **5k**	35	69
12	 **5l**	35	88^b
13^b	 **5m**	75	81^{b,c}
14	 **5n**	35	89^b
15	 **5o**	40	89
16	 **5p**	40	45^d
17	 **5q**	55	30^{e,f}
18	 **5r**	40	95^b

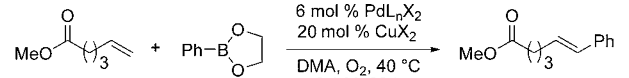
[a] Yields are averages of two experiments performed on a 0.5 mmol scale. The selectivity for (*E*)-styrene was >20:1 unless otherwise noted. [b] Selectivity for (*E*)-styrene was 10:1. [c] Using 10 mol % $\mathrm{Pd(I^iPr)(OTs)_2}$. [d] Recovered 44% starting material. [e] Selectivity for (*E*)-styrene was 6:1. [f] The remainder of the mass balance for this reaction was mainly recovered starting material

conditions, giving a yield of only 30%. Notably, an enantiomerically enriched substrate was subjected to the reaction conditions (eq 4) with no erosion in enantiomeric excess, further demonstrating this reaction's potential utility in organic synthesis.



1a (>99% ee) **4a** (3 equiv) **5a** (>99% ee) (4)

Table 3. Common Pd^{II} Salts in the Oxidative Heck Reaction



1l **4a** (3 equiv) **5r**

entry	Pd^{II} source	Cu^{II} source	% conversion^a	% yield^a	selectivity^b
1	$\mathrm{Pd(MeCN)_2Cl_2}$	$CuCl_2$	15.3	>1	–
2	$\mathrm{Pd(OAc)_2}$	$\mathrm{Cu(OAc)_2}$	>99	35.3	6.2:1
3	$\mathrm{Pd(OAc)_2}$	$\mathrm{Cu(OTf)_2}$	>99	55.7	2.0:1
4	$\mathrm{Pd(MeCN)_2(OTs)_2}$	$\mathrm{Cu(OTf)_2}$	>99	99	3.4:1
5	$\mathrm{[Pd(I^iPr)Cl_2]_2}$	$\mathrm{Cu(OTf)_2}$	79.6	60.8	4.4:1
6	$\mathrm{Pd(I^iPr)(OTs)_2}$	$\mathrm{Cu(OTf)_2}$	>99	96.3	9.8:1

[a] Conversion and yield were calculated by comparing starting material and product peak integrations to the integration for an internal standard using GC analysis. Each reported yield is the sum for all of the isomers. [b] The selectivity is **5r**:(all other isomers), as determined by GC analysis.

In order to demonstrate that the high selectivity observed under these conditions is attributable to the $\mathrm{Pd(I^iPr)(OTs)_2}$ catalyst, we submitted substrate **1l**, which is highly susceptible to the formation of undesired isomeric products, to similar conditions using more traditional catalysts (Table 3).[7] The reaction did not proceed when chloride was used as the counterion on palladium and copper (entry 1), whereas the acetate anion was more effective, delivering the product in diminished selectivity in comparison with our system (entry 2 vs 6). Using $\mathrm{Pd(OAc)_2}$ or $\mathrm{Pd(MeCN)_2(OTs)_2}$ in conjunction with $\mathrm{Cu(OTf)_2}$ resulted in the precipitation of Pd(0) (entries 3 and 4), and while the $\mathrm{[Pd(I^iPr)Cl_2]_2}$ catalyst did not decompose in the presence of $\mathrm{Cu(OTf)_2}$, the reaction proceeded more sluggishly (entry 5 vs 6). These results suggest that both a highly electrophilic palladium and the stabilizing ligand are crucial for selective and high-yielding catalysis.

In view of the unusually high selectivity observed in this oxidative Heck reaction, we wished to gain insight into the mechanistic origin of the selectivity. Specifically, we wished to probe whether the hydrogen atom undergoing β-hydride elimination in the selectivity-determining step displayed protic, hydridic, or hydrogen-atom-like character. To accomplish this, β,γ-unsaturated ester **1l** was subjected to the reaction conditions with electronically disparate arylboronic esters. This experiment probed the partitioning of intermediate **X** via β-hydride elimination of either H_A or H_S (Figure 1). Plotting the logarithm of the ratio of products $\mathbf{5_A}$ and $\mathbf{5_S}$ versus the Hammett σ value for the arylboronic ester substituent resulted in an unusual Hammett correlation wherein a break in linearity at $\sigma = 0$ (R = H) was revealed.[8,9]

Typically, a Hammett correlation of this type is attributed to a change in reaction mechanism. In this case, electron-rich arenes favor the styrenyl product in comparison with phenyl, wherein the electron donor on the arene supports a buildup of positive charge that results in a classic hydridic delivery of H_S to Pd. Surprisingly, electron-poor arenes also favor the styrenyl product relative to phenyl. On the basis of a change-in-mechanism analysis, a possible explanation is that electron-poor substituents stabilize a developing negative charge at the benzylic site, implying that the loss of H_S is more protic in nature. However, if acidity dominates the product ratio, one would expect to observe the α,β-unsaturated ester as the overwhelming product, since the pK_a of protons α to an ester is substantially lower than that of toluene.[10] Another interesting possibility is that the strength of the C–H bond dictates the product distribution in this reaction. Indeed, both electron-donating and electron-withdrawing substituents have been reported to stabilize radicals on toluene derivatives relative to toluene itself.[11] While this analysis is clearly in the preliminary stages, the electrophilic

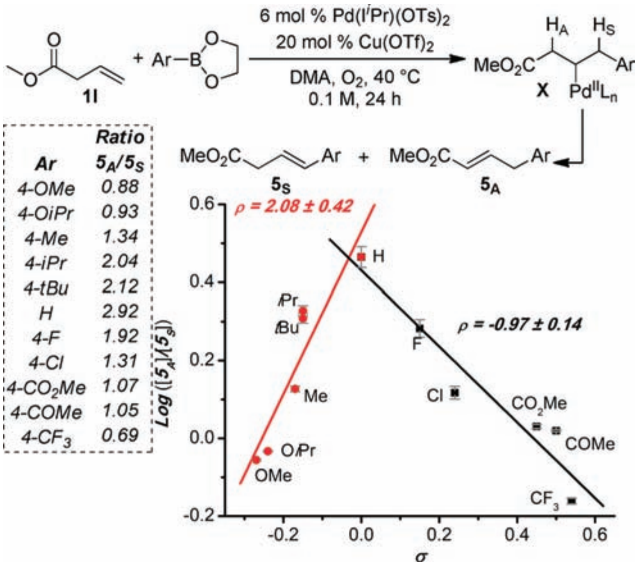


Figure 1. Hammett plot.

nature of the catalyst coupled with the exceptional observed selectivity for benzylic C−H bond abstraction is highly suggestive of this hypothesis.

In conclusion, we have reported the first oxidative Heck reaction to deliver high selectivity for (*E*)-styrenyl products without the requirement that particular functionality be present in the substrate. This reaction is generally high-yielding and tolerant of diverse functionality and performs well under mild reaction conditions with no need for base or high temperatures. The nature of β-hydride elimination in the selectivity-determining step was probed through product partitioning analysis. Two linear free-energy relationships, depending on the electronic nature of the boronic ester, were obtained from these studies, suggesting that the selectivity may be governed by the C−H bond strength. Given the unexpected nature of this result, we plan to study the mechanism of this transformation and determine the factors that result in high selectivity for styrenyl products. These investigations are currently underway in our laboratory.

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Supporting Information Available: Optimization data, experimental procedures, and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(2) For examples of the oxidative Heck reaction, see: (a) Jia, C.; Piao, D.; Oyamada, J.; Lu, W.; Kitamura, T.; Fujiwara, Y. *Science* **2000**, *287*, 1992–1995. (b) Du, X.; Suguro, M.; Hirabayashi, K.; Mori, A.; Nishikata, T.; Hagiwara, N.; Kawata, T.; Okeda, T.; Wang, H. F.; Fugami, K.; Kosugi, M. *Org. Lett.* **2001**, *3*, 3313–3316. (c) Parrish, J. P.; Jung, Y. C.; Shin, S. I.; Jung, K. W. *J. Org. Chem.* **2002**, *67*, 7127–7130. (d) Jung, Y. C.; Mishra, R. K.; Yoon, C. H.; Jung, K. W. *Org. Lett.* **2003**, *5*, 2231–2234. (e) Andappan, M. M. S.; Nilsson, P.; von Schenck, H.; Larhed, M. J. *J. Org. Chem.* **2004**, *69*, 5212–5218. (f) Yoo, K. S.; Yoon, C. H.; Jung, K. W. *J. Am. Chem. Soc.* **2006**, *128*, 16384–16393. (g) Jia, C.; Piao, D.; Oyamada, J.; Lu, W.; Kitamura, T.; Fujiwara, Y. *Science* **2000**, *287*, 1992–1995. (h) Zhang, Y.-H.; Shi, B.-F.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 5072–5074. (i) Zhang, X.; Fan, S.; He, C.-Y.; Wan, X.; Min, Q.-Q.; Yang, J.; Jiang, Z.-X. *J. Am. Chem. Soc.* **2010**, *132*, 4506–4507.

(3) Delcamp, J. H.; Brucks, A. P.; White, C. M. *J. Am. Chem. Soc.* **2008**, *130*, 11270–11271.

(4) Additional byproducts can arise from Heck insertion in the opposite orientation, resulting in terminal olefin products and internal olefin isomeric products arising from Pd−H migration. (*Z*)-Olefin isomers may also be observed.

(5) (a) Werner, E. W.; Urkalan, K. B.; Sigman, M. S. *Org. Lett.* **2010**, *12*, 2848–2851. (b) Urkalan, K. B.; Sigman, M. S. *Angew. Chem., Int. Ed.* **2009**, *48*, 3146–3149.

(6) Submission of the corresponding allylic chloride resulted in no reaction.

(7) Use of substrate **1l** under the chelation-controlled conditions reported in ref 3 resulted in a 1.2:1 mixture, as determined by ^{1}H NMR integration.

(8) For examples of Hammett analyses of other Heck reactions, see: (a) Benhaddou, R.; Czernecki, S.; Ville, G.; Zegar, A. *Organometallics* **1988**, *7*, 2435–2439. (b) Fristrup, P.; Le Quement, S.; Tanner, D.; Norrby, P. O. *Organometallics* **2004**, *23*, 6160.

(9) As a control experiment, a mixture of $\mathbf{5_A}$ and $\mathbf{5_S}$ was submitted to a separate oxidative Heck reaction to form **5e** wherein no change in the ratio was observed.

(10) Protons α to esters have a pK_a values of $\sim$25, while the pK_a of toluene is 38.

(11) Wu, Y.-D.; Wong, C.-L.; Chan, K. W. K. *J. Org. Chem.* **1996**, *61*, 746–750.

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