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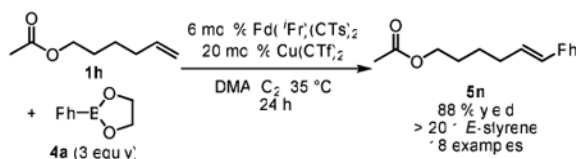
A Highly Selective and General Palladium Catalyst for the Oxidative Heck Reaction of Electronically Non-Biased Olefins

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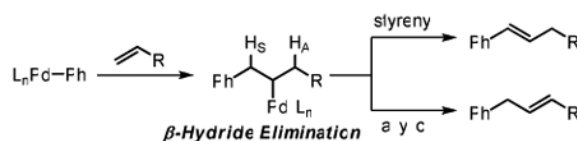
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Abstract



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 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 catalysts 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 C-C bond under 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 coworkers, is proposed to rely on substrate chelation to afford these products as the only observable isomer.³ The poor selectivity under typical Heck conditions presumably arises from a lack of the metal center's 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.



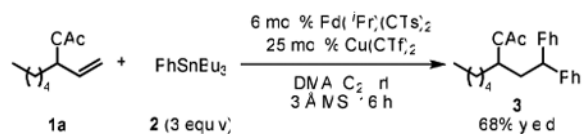
(1)

Recently, we reported an olefin diarylation reaction which utilizes the oxidative Heck mechanistic manifold, but intercepts reactive Pd^{II}-alkyl intermediates with an aryl stannane

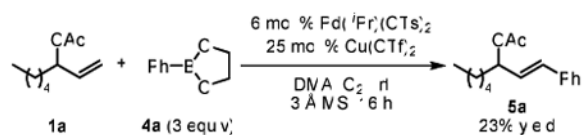
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Supporting Information **Available:** Optimization data, experimental procedures, and characterization data. This material is available free of charge via the Internet at <http://pubs.acs.org>

in a second transmetalation event (eq. 2).⁵ The success of this system was partially attributed to the cationic nature of the catalyst. Considering the ubiquitous nature of aryl boronic acid derivatives in cross coupling, we choose to evaluate these in our alkene difunctionalization reactions. To our surprise, the use of phenyl boronic ester **4a** in the place of the PhSnBu_3 resulted in only *E*-styrenyl Heck product **5a** with no diarylation or isomeric products observed.



(2)



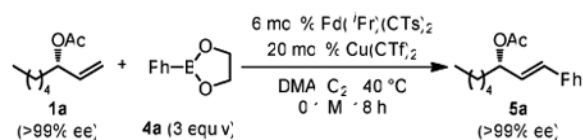
(3)

Optimization of this reaction was performed, wherein raising the temperature to 40 °C resulted in improved yield without diminishing selectivity. Removing molecular sieves and decreasing the $\text{Cu}(\text{OTf})_2$ loading further improved the GC yield to >99% in >20:1 selectivity for the *E*-styrenyl isomer (Table 1). Finally performing the reaction in the absence of the Pd^{II} catalyst, $\text{Cu}(\text{OTf})_2$ 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 0.5 mmol scale resulted in 95% yield of the desired product (Table 2, entry 1).⁶

Considering 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 (entries 2-3). A substrate containing a TBS-protected homoallylic alcohol gives good yields and high selectivity for a range of arylboronic esters (entries 4-7).

A free homoallylic alcohol is 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 aryl boronic ester required increased catalyst loading and elevated temperatures, resulting in a reduction of selectivity (entry 13, 10:1 olefin isomers). An acetonide-protected diol is an excellent substrate even though a Lewis acidic catalyst is used (entry 14). Nitrogen containing substrates were incompatible with previously reported reactions utilizing this catalyst, but an allylic amine with two carbamate protecting groups (entry 15) performed well in the reaction. However, a more electron rich carbamate leads 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 conditions, giving only 30% yield. Of note, 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.



(4)

In order to demonstrate that the high selectivity observed under these conditions is attributable to the $\text{Pd}(\text{I}^i\text{Pr})(\text{OTf})_2$ catalyst we submitted substrate **11**, which is highly susceptible to the formation of undesired isomeric products, to similar conditions using more traditional catalysts (Table 3).⁷ The reaction does not proceed when chloride is used as the counterion on palladium and copper (entry 1), whereas the acetate anion is more effective, delivering the product in diminished selectivity as compared to our system (entry 2 vs 6). Using $\text{Pd}(\text{OAc})_2$ or $\text{Pd}(\text{MeCN})_2(\text{OTf})_2$ in conjunction with $\text{Cu}(\text{OTf})_2$ results in the precipitation of $\text{Pd}(0)$ (entries 3 and 4) while the $\text{Pd}(\text{I}^i\text{Pr})\text{Cl}_2$ catalyst does not decompose in the presence of $\text{Cu}(\text{OTf})_2$, but proceeds 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.

Considering 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 **11** was subjected to the reaction conditions with electronically disparate arylboronic esters. This experiment probes the partitioning of intermediate **X** via β -hydride elimination of either H_A or H_S (Figure 1). Plotting the log of the ratio of products **5_A** and **5_S** versus Hammett σ values for the corresponding aryl boronic ester substituent results in an unusual Hammett correlation wherein a break in linearity at $\sigma = 0$ is revealed ($R = 0.89$).

Typically, a Hammett correlation of this type is attributed to a reaction mechanism change. In this case, electron rich arenes favor the styrenyl product as compared to phenyl wherein the electron donor on the arene supports positive charge buildup resulting in a classic hydridic delivery of H_S to Pd. Surprisingly, electron poor arenes also favor the styrenyl product relative to phenyl. Using a change in mechanism analysis, a possible explanation is that electron poor substituents are stabilizing a developing negative charge at the benzylic site implicating 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 esters is substantially lower than that of toluene.¹⁰ Another interesting possibility is that the strength of the C-H bond is dictating the product distribution in this reaction. Indeed, both electron donating and electron withdrawing substituents have been reported to stabilize radicals on toluene derivatives as compared to toluene itself.¹¹ While this analysis is clearly in the preliminary stages, the electrophilic 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 report the first oxidative Heck reaction to deliver high selectivity for *E*-styrenyl products without the requirement for particular functionality present in the substrate. This reaction is generally high yielding, 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, dependent on the electronic nature of the boronic ester, result 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

1. For reviews of the Heck Reaction see: (a) Heck RF. *Org React.* 1982; 27:345–390. (b) Beletskaya IP, Cheprakov AV. *Chem Rev.* 2000; 100:3009–3066. [PubMed: 11749313] (c) Whitcombe NJ, Hii KK, Gibson SE. *Tetrahedron.* 2001; 57:7449–7476. (d) Kondolff I, Doucet H, Santelli M. *Tetrahedron Lett.* 2003; 44:8587–8491.
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. [PubMed: 10720319] (b) Du X, Suguro M, Hirabayashi K, Mori A, Nishikata T, Hagiwara N, Kawata T, Okeda T, Wang HF, Fugami K, Kosugi M. *Org Lett.* 2001; 3:3313–3316. [PubMed: 11594822] (c) Parrish JP, Jung YC, Shin SI, Jung KW. *J Org Chem.* 2002; 67:7127–7130. [PubMed: 12354008] (d) Jung YC, Mishra RK, Yoon CH, Jung KW. *Org Lett.* 2003; 5:2231–2234. [PubMed: 12816416] (e) Andappan MMS, Nilsson P, von Schenck H, Larhed MJ. *J Org Chem.* 2004; 69:5212–5218. [PubMed: 15287763] (f) Yoo KS, Yoon CH, Jung KW. *J Am Chem Soc.* 2006; 128:16384–16393. [PubMed: 17165795] (g) Jia C, Piao D, Oyamada J, Lu W, Kitamura T, Fujiwara Y. *Science.* 2000; 287:1992–1995. [PubMed: 10720319] (h) Zhang YH, Shi BF, Yu JQ. *J Am Chem Soc.* 2009; 131:5072–5074. [PubMed: 19296661] (i) Zhang X, Fan S, He CY, Wan X, Min QQ, Yang J, Jiang ZX. *J Am Chem Soc.* 2010; 132:4506–4507. [PubMed: 20225875]
3. Delcamp JH, Brucks AP, White CM. *J Am Chem Soc.* 2008; 130:11270–11271. [PubMed: 18671350]
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 EW, Urkalan KB, Sigman MS. *Org Lett.* 2010; 12:2848–2851. [PubMed: 20481606] (b) Urkalan KB, Sigman MS. *Angew Chem, Int Ed.* 2009; 48:3146–3149.
6. Submission of the corresponding allylic chloride resulted in no reaction.
7. Use of substrate **11** under the chelation controlled conditions reported in reference 3 result in a 1.2:1 mixture as determined by ^1H 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 PO. *Organometallics.* 2004; 23:6160.
9. As a control experiment, a mixture of **5A** and **5S** was submitted to a separate oxidative Heck reaction to form **5e** where no change in the ratio was observed.
10. Protons α to an ester have a $\text{p}K_{\text{A}}$ around 25, while toluene's $\text{p}K_{\text{A}}$ is 38.
11. Wu YD, Wong CL, Chan KWK. *J Org Chem.* 1996; 61:746–750. [PubMed: 11666999]

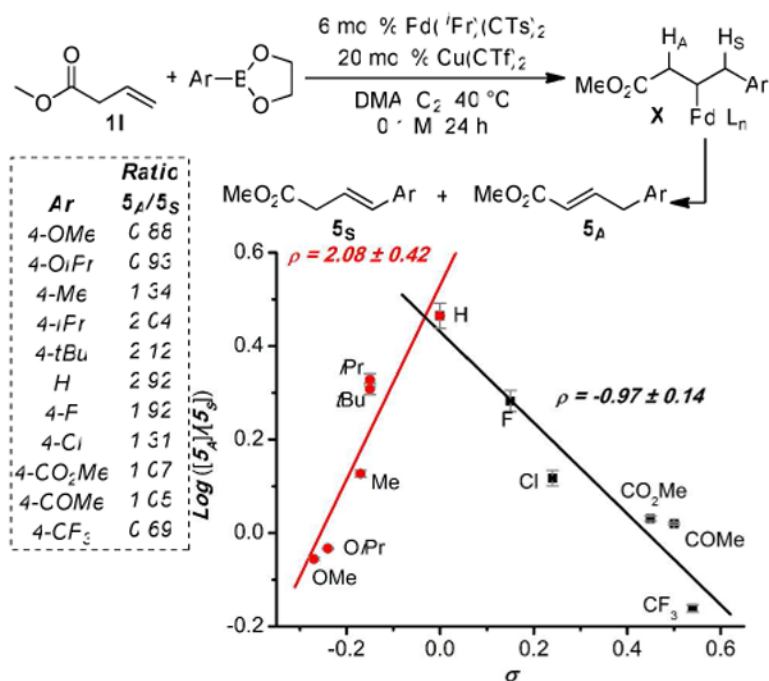
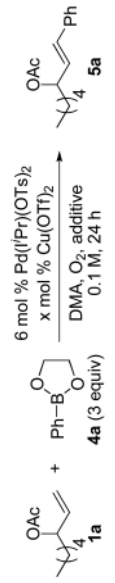


Figure 1.
Hammett plot.

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 calculated by comparing starting material and product peak integration to integration of internal standard using GC analysis.

^b No Pd(I(Pr)(OTf)2) was used.

^c Reaction was run under nitrogen.

Table 2

Scope of the oxidative Heck reaction.

entry	product	temperature	% yield ^a
1	5a	40	95
2		45	97
3		45	73
4		35	81
5		35	80
6		45	87
7		45	78
8		40	63 ^b
9		35	80 ^b
10		35	89 ^b
11		35	69
12		35	88 ^b
13 ^b		75	81 ^{b,c}
14		35	89 ^b
15		40	89
16		40	45 ^d

entry	product	temperature	% yield ^a
17	 5q	55	30 ^{e,f}
18	 5r	40	95 ^b

^aYield is average of two experiments performed on 0.5 mmol scale. Selectivity for *E*-styrene > 20:1 unless otherwise noted.

^bSelectivity for *E*-styrene is 10:1.

^c10 mol % Pd(IⁱPr)(OTs)₂ used.

^dRecovered 44% starting material.

^eSelectivity for *E*-styrene is 6:1.

^fThe remainder of the mass balance for this reaction is mainly recovered starting material

Common Pd^{II} salts in the oxidative Heck reaction.

^a Conversion and yield calculated by comparing starting material and product peak integration to integration of internal standard using GC analysis. Yield reported is the sum of all isomers.

^b Selectivity is **5r**:all other isomers as determined by GC analysis.