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Single-step synthesis of styryl phosphonic acids *via* palladium-catalyzed Heck coupling of vinyl phosphonic acid with aryl halides†

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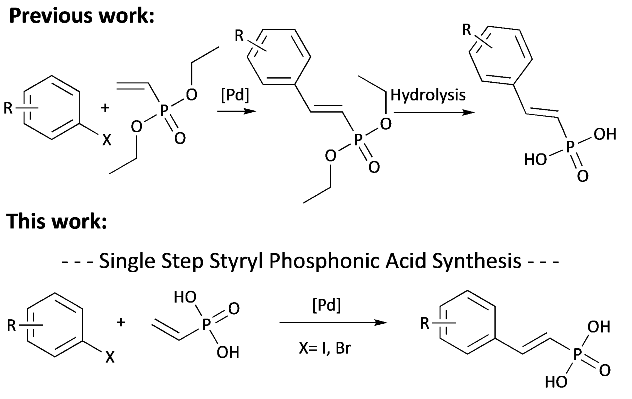
We have developed a single step palladium-catalyzed Heck coupling of aryl halides with vinyl phosphonic acid to produce functionalized (*E*)-styryl phosphonic acids. This pathway utilizes a variety of commercially available aryl halides, vinyl phosphonic acid and $Pd(P(tBu)_3)_2$ as catalyst. These conditions produce a wide range of styryl phosphonic acids with high purities and good to excellent yields (31–80%).

The palladium catalyzed Heck reaction is a powerful synthetic tool in both simple and complex organic syntheses, the topic of thousands of publications, and part of the 2010 Nobel prize in chemistry.[1–3] Recently the Heck coupling of aryl halides with acrylic acid to produce functionalized cinnamic acid derivatives for applications in tuning electrode interfacial surface energetics have been reported.[4–7] However, a thorough survey of the literature reveals that styryl phosphonic acid analogues of cinnamic acids are quite rare.[8–11]

The broad utility of phosphonic acid ligands have been studied and reviewed for the tuning of electrode work functions, surface energies, and electron charge transfer kinetics.[12,13] These modifications with phosphonic acid ligands have led to increased efficiency and operational range in organic-based devices, such as organic light emitting diodes (OLEDs), organic photovoltaic (OPVs), and most recently perovskite solar cells.[8–11,14–20] Much of this effect is attributed to the conjugated linkage between the acid group (binding site) and the functional aromatic ring. For example, upon binding to a surface through the phosphonic acid group the dipole on the aromatic ring can better communicate to the surface through the conjugated linkage. Thus, when the acid is bound to the surface of an electrode a rather large tuning of the electrode has been observed which has been shown to have modest improvement in the power conversion efficiency of inverted P3HT:ICBA solar cells.[6,21]

Despite these promising results very few of these acids are commercially available, which has led us to explore a route for their simple, high yield, and cost-effective synthesis. In general, the current synthetic route of synthesizing these styryl phosphonic acid ligands is a two-step mechanism. First, the Heck coupling of aromatic halide with diethyl vinylphosphonate yielding the intermediate diethyl (*E*)-styryl phosphonate followed by column purification, and second, the hydrolysis of the dialkyl esters which requires harsh conditions utilizing reagents such as trimethylsilyl halides or refluxing in concentrated inorganic acids. These rather harsh conditions are not tolerant of functional groups and often lead to poor yields (Scheme 1 – previous work).[10,16,22,23] In addition, final products were often slightly discolored, indicating the possibility of impurities despite characterization showing high purity, *i.e.* NMR, GCMS. It has been well established that the slightest impurities could lead to reduced performance or lifetime of OLED, OPV or perovskite devices.[24,25] Thus, there is a need to develop efficient methods for the direct high yield synthesis of highly pure and functionalized styryl phosphonic acids. Herein we report the highly stereo-selective



Scheme 1 Palladium-catalyzed styryl phosphonic acid general synthesis.

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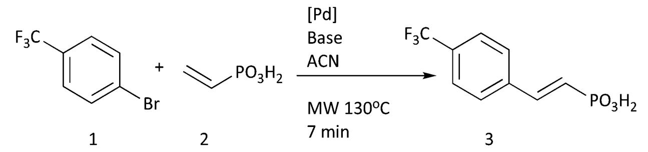

Scheme 2 Model reaction for synthesis of CF_3VPA.

Heck coupling of vinyl phosphonic acid with commercially available aryl halides to form styryl phosphonic acids in good yields. (Scheme 1 – this work)

We began our investigation with a model reaction of 4-bromobenzotrifluoride (**1**) and vinyl phosphonic acid (**2**), which were coupled under microwave conditions to form product (**3**) (*E*)-(4-(trifluoromethyl) styryl) phosphonic acid, CF_3VPA (Scheme 2). The CF_3VPA product was selected as the model reaction because we found in our previous work that the workup and purification is relatively simple. Upon reaction completion, the product mixture was first treated in a standard acidic aqueous (5% HCl/vol) organic (ethyl acetate – EA) extraction. Then, the organic fraction was dried with magnesium sulfate, filtered, and the filtrate was concentrated under rotory evaporation to a volume of only a few milliliters. Finally, product **3** (CF_3VPA) was isolated by precipitation into dichloromethane (DCM) and recovered by filtration, producing a bright white powder with purity determined by GCMS and NMR.

To find a suitable catalytic system for the synthesis of VPA, we evaluated various Pd catalysts (*e.g.*, $Pd(P(tBu)_3)_2$, $Pd(PPh_3)_4$, Pd(dba)/TPP, Herrmann's palladacycle, and $Pd(OAc)_2$). Results showed that only $Pd(P(tBu)_3)_2$ provided any measurable yield of the desired product, so we moved forward with this particular catalyst to prepare more acids.[26] We found that all other catalysts led to no recoverable yield, specifically no product was formed in any detectable quantity (*e.g.* TLC, GCMS, NMR, HRMS).

In tandem, we investigated the influences of various bases on the reaction. As shown in Table 1, the selected bases did not have any effect on the reactivity of the Pd catalyst systems. In addition, we noted a slight increase in yield (Table 1, entry 1) when utilizing NCy_2Me, over TEA or Cs_2CO_3 with $Pd(P(tBu)_3)_2$.

Finally, to fully optimize reaction conditions, we investigated the influence of various polar solvents (*e.g.* acetonitrile (ACN), dioxane, tetrahydrofuran (THF)) on the reaction yield. For this reaction optimization we considered only polar solvents, as VPA does not readily dissolve in non-polar solvents such as toluene. Although ACN, dioxane, and THF all performed similarly, we selected THF as it was the best solvent with regard to solubilizing a wide variety of aromatic halides. After evaluating many reaction conditions we selected microwave conditions of 7 minutes at 130 °C (Table 2).

Table 1 Catalyst selection of vinyl phosphonic acid with 4-bromobenzotrifluoride

Entry	Catalyst	Solvent	Base (TEA)	Base (Cs_2CO_3)	Base (NCy_2Me)
1	$Pd(P(tBu)_3)_2$	ACN	63%	65%	66%
2	$Pd(PPh_3)_4$	ACN	NR	NR	—
3	Pd(dba)/TPP	ACN	NR	NR	—
4	Herrmann's	ACN	NR	NR	—
5	$Pd(OAc)_2$/TPP	ACN	NR	NR	—

Reaction conditions: **1** (1 mmol), **2** (1.1 mmol), Pd cat. (10 mol%), base (1.1 mmol) and 3 mL of anhydrous ACN, for Pd(II) systems TPP ligand was introduced at 20 mol%. Reaction was microwaved for 7 minutes at 12 bar and 130 °C with stirring. Yield is the average of two reactions.

Table 2 Solvent optimization in microwave conditions

Entry	Catalyst	Base	Solvent	Yield (%)
6	$Pd(P(tBu)_3)_2$	NCy_2Me	ACN	66
7	$Pd(P(tBu)_3)_2$	NCy_2Me	Dioxane	67
8	$Pd(P(tBu)_3)_2$	NCy_2Me	THF	68

Reaction conditions: **1a** (1 mmol), **1b** (1.1 mmol), $Pd(P(tBu)_3)_2$, (10 mol%), NCy2Me (1.1 mmol) and 3 mL of anhydrous solvent were microwaved for 7 minutes at 12 bar and 130 °C with stirring. Yield is the average of two reactions.

We then studied the Heck coupling reaction as a consequence of electron withdrawing and donating groups on the aromatic halides. As shown in Fig. 1, products were prepared in moderate to good yields. With the exception of products **9–11**, products were confirmed *via* GCMS; however, they were inseparable from the crude reaction. The highly fluorinated products **3**, **4** and **8** were

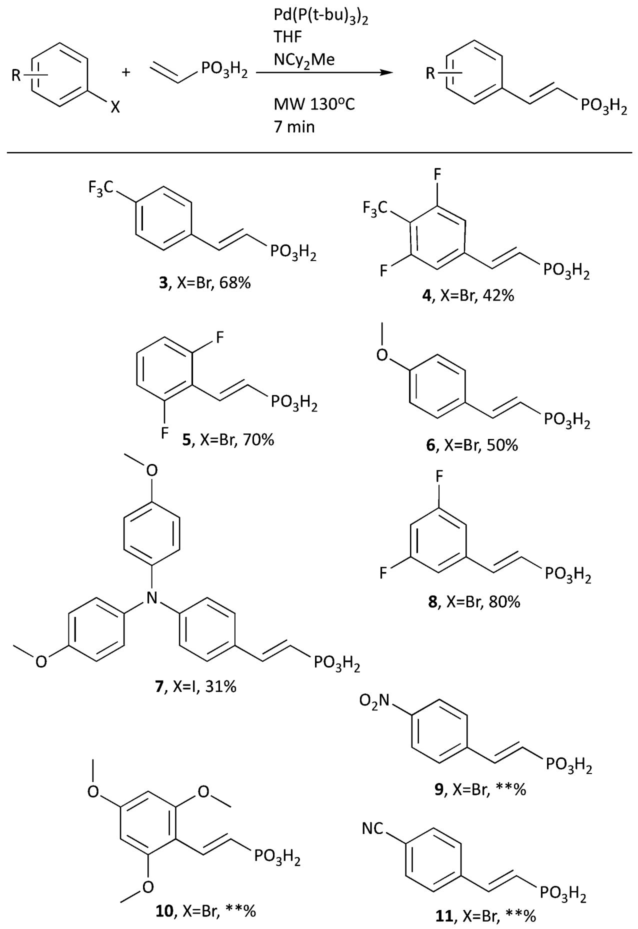

Fig. 1 Optimized single step Heck coupling with substrate (top) and scope of synthesized styryl phosphonic acids using VPA and aromatic halides. (bottom) Reaction conditions: aromatic halide (1 mmol), vinyl phosphonic acid (1.1 mmol), $Pd(P(tBu)_3)_2$ (10 mol%), NCy_2Me (1.1 mmol) and 3 mL of anhydrous THF were microwaved for 7 minutes at 12 bar and 130 °C with stirring. Yield is the average of two reactions. ** products were inseparable from reaction crude.

easily separated through a precipitation process as described in detail in the ESI.† Furthermore, these isolated products were white powders, indicating a higher purity when compared to the hydrolysis products of Scheme 1 – previous work, which were reported to have slight off-white color.[16,21]

Products **5** and **6** were obtained from extraction and ultimately recrystallized in ACN, and **7** from flash chromatography; further purification details and information can also be found in the ESI.† Notably, in all of the purified products a trace amount of the (*Z*)-isomer is detectable (see ESI† selected NMR spectra). Generally the $Pd(P(tBu)_3)_2$ combined with NCy_2Me produced the (*E*)-isomer, however we do note a consistent ≈20/1 *E*/*Z* ratio. This potentially could be improved with minor changes to the base or solvent systems, but this high *E*/*Z* stereoisomer selectivity is consistent with similar cinnamic analogues under these reaction conditions.[4,7,27]

Additionally, products **3–5**, and **8** were scaled up to 10 gram reactions using traditional hotplate and Schlenk line techniques, as this amount exceeded the capability of our microwave reactor. Here, a 50 mL flask was evacuated and purged with argon 3×, then the solid reactants were added to the flask. The flask was then evacuated and argon refilled 3× and the liquid reactants and solvent were added. The reaction was heated to 65 °C with stirring until the reaction was complete as determined from TLC (12–48 hours). These large-scale reactions provided similar yields to the microwave approach even when the catalyst was reduced to 1 mol%.

In conclusion, we have developed a practical and original set of conditions for the direct palladium-catalyzed coupling of aromatic halides with vinyl phosphonic acid to form new (*E*)-styryl phosphonic acids. This method produces the target molecules in moderate to good yields from a variety of electron donating or withdrawing aromatic halides resulting in high purity products when compared to other methods. Our reaction conditions use both traditional or microwave heating and are fully scalable to gram size reactions with high purity and product yields. We anticipate that our protocol has a number of applications where introduction of the vinyl phosphonic acid group may be desired.

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Conflicts of interest

There are no conflicts to declare.

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