SUPPLEMENTARY INFORMATION

Single-Step Synthesis of Styryl Phosphonic Acids via Palladium-Catalyzed Heck Coupling of Vinyl Phosphonic Acid with Aryl Halides

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Experimental Methods

All chemicals were used as received without further purification unless noted. Acetonitrile (ACN, ACS) dichloromethane (DCM, ACS), anhydrous tetrahydrofuran (THF, ≥99.9%), N,N-dicyclohexylmethylamine (NCy2Me, 97%), and anhydrous magnesium sulfate (MgSO4), were obtained from Sigma Aldrich. Sodium hydroxide (NaOH, Pearl 97%) was obtained from Fisher Scientific. Bis(tri-tert-butylphosphine)palladium (Pd[P(t-Bu)3]2, 98%) was obtained from Strem Chemical. Vinyl phosphonic acid (95%) was obtained from TCI Chemicals. Hydrochloric acid (HCl, ACS) was obtained from Macron Fine Chemicals. All glassware was base, acid, and water washed then oven dried. 1H, 13C, 19F, and 31P NMR, spectra were obtained on a JEOL ECA 500 liquid-state NMR spectrometer and data obtained was manipulated in MestReNova NMR processor software. Microwave synthesis was preformed on a Biotage Initiator+ microwave system. Flash chromatography was preformed on a Biotage Isolara Prime flash chromatography system with Biotage Snap Ultra or Biotage Snap Kp-sil cartridges. High-resolution mass spectrometry (HRMS) was preformed using a JEOL JMS-700T The TandemMStation by a direct probe injection. The samples were ionized by positive electron ionization (EI+) and the spectrum was generated by linear ejection fraction (EF-Linear). All samples were calibrated by an internal standard of Perfluorokerosene-H (PFK, Alfa Aesar Lot #C03T024). The ion peak and the predicted ion peak are located in the Table S1 below.
Phosphonic Acid synthesis

**Microwave phosphonic acid synthesis** – Under ambient air a 20 mL Biotage microwave vial equipped with a magnetic stir bar was charged with the aromatic halide, vinyl phosphonic acid, N,N-dicyclohexylmethylamine, Pd[P(t-Bu)_3]_2 (catalyst used at 1 mol % level), and THF. The mixture was heated to 180°C at 12 Bar for 15 min, upon completion and cooling workup followed crude PA purification below.

**Traditional phosphonic acid synthesis** - A Schlenk flask equipped with a magnetic stir bar under argon was charged with the aromatic halide, vinyl phosphonic acid, N,N-dicyclohexylmethylamine, Pd[P(t-Bu)_3]_2 (catalyst used at 1 mol % level), and THF. The mixture was heated to 70°C for 24 h and periodically tested via TLC for reaction completion, upon completion and cooling followed crude PA purification below.

**Crude phosphonic acid purification** - The crude product mixture was extracted three times with ethyl acetate and acidic water (5% HCl). The organic layer was dried with MgSO_4_, filtered, and the solvent removed using a rotary evaporator. The resultant product was then further purified by recrystallization in ACN or precipitation in DCM.

3 - (E)-(4-(trifluoromethyl)styryl)phosphonic acid -

Synthesis followed microwave PA synthesis procedure above, utilizing 4-(trifluoromethyl) bromobenzene as the aromatic halide. However, as noted in the main text, purification of the reaction crude was first treated in an acidic aqueous (5% HCl/vol) organic EA extraction. Then, the organic fraction was dried with magnesium sulfate, and the solvent was concentrated under rotary evaporation to a volume of only a few milliliters. Finally, 3 was isolated by precipitation into DCM and filtration producing a bright white powder. This compound has been previously synthesized and reported\(^1\)\(^,\)\(^2\) and the \(^1\)H NMR (Figure S1) and HRMS (Table S1) characterization matches appropriately.

\(^1\)H NMR (500 MHz, DMSO-\(d_6\)) \(\delta\) 7.80 (s, 2H), 7.71 (s, 2H), 7.26 (dd, 1H), 6.65 (dd, 1H), 5.72 (s, 2H).
4 - (E)-(3,5-difluoro-4-(trifluoromethyl)styryl)phosphonic acid

Synthesis followed the microwave PA synthesis procedure above, utilizing (3,5-difluoro-4-(trifluoromethyl) bromobenzene as the aromatic halide. However, as noted in the main text, purification of the reaction crude was first treated in an acidic aqueous (5% HCl/vol) organic EA extraction. Then, the organic fraction was dried with magnesium sulfate, and the solvent was concentrated under rotory evaporation to a volume of only a few milliliters. Finally, 4 was isolated by precipitation into DCM and filtration producing white flakes. To our knowledge this is a novel compound. See Figures S2-S5 for corresponding NMR spectra and HRMS (Table S1).

$^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 7.71 (d, $J = 11.6$ Hz, 2H), 7.14 (dd, $J = 21.2$ Hz, 1H), 6.84 (dd, $J = 17.4$, 14.7 Hz, 1H), 5.72 (s, 2H).

$^{13}$C NMR (126 MHz, DMSO-$D_6$) $\delta$ 167.37, 160.68-158.64 (D $J_{C-P}$ =160Hz 1C), 142.52, 140.36, 125.54 (2C), 123.10-120.93 (d, $J_{C-\beta}$ 122Hz 1C) 113.27, 113.08, 39.92.

$^{19}$F NMR (471 MHz, DMSO-$D_6$) $\delta$ -55.20, -112.07.

$^{31}$P NMR (202 MHz, DMSO-$D_6$) $\delta$ 11.85.

5 - (E)-(2,6-difluorostyryl)phosphonic acid

Synthesis followed the microwave PA synthesis procedure above utilizing 2,6-difluorobenziodobenzene as the aromatic halide. However, as noted in the main text, purification of the reaction crude was first treated in an acidic aqueous (5% HCl/vol) organic EA extraction. Then, the organic fraction was dried with magnesium sulfate, and the solvent was concentrated under rotor evaporation to a volume of only a few milliliters. Finally, 5 was isolated by precipitation into DCM and filtration yielding brilliantly white flakes. This compound has been previously synthesized and reported$^1, 2$, NMR (Figure S6) and HRMS (Table S1) and characterization matches appropriately.

$^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 10.06 (s, 1H), 7.43 (t, $J = 9.6$ Hz, 1H), 7.21 – 7.07 (m, 3H), 6.54 (t, $J = 17.5$ Hz, 1H).
6 - (E)-(4-methoxystyryl)phosphonic acid
Synthesis followed the microwave PA synthesis procedure above utilizing 4-bromoanisole as the aromatic halide. This compound has been previously synthesized and reported\(^1\,^2\) and the \(^1\)H NMR characterization matches appropriately (Figure S7).
\(^1\)H NMR (500 MHz, DMSO-\(d_6\)) \(\delta\) 7.51 (d, \(J = 8.7\) Hz, 2H), 7.09 (dd, \(J = 21.9, 17.4\) Hz, 1H), 6.91 (d, \(J = 8.7\) Hz, 2H), 6.27 (t, \(J = 16.9\) Hz, 1H), 3.74 (s, 3H).

7 - (E)-(4-(bis(4-methoxyphenyl)amino)styryl)phosphonic acid
Synthesis followed the traditional PA synthesis procedure above utilizing 4-iodo-4',4''-dimethoxytriphenylamine as the aromatic halide, with the exception that once the crude was isolated after extraction, flash chromatography was used to isolate 130mg (31% yield) of a bright yellow highly fluorescent product. To our knowledge this is a novel compound. See Figures S8-S10 for corresponding NMR spectra.
\(^1\)H NMR (500 MHz, DMSO-\(d_6\)) \(\delta\) 7.15 – 6.98 (m, 2H), 6.97 – 6.84 (m, 4H), 6.79 (d, \(J = 14.0\) Hz, 4H), 6.69 (d, \(J = 27.2\) Hz, 2H), 6.27 – 6.07 (m, 1H), 3.71 – 3.63 (m, 6H).
\(^13\)C NMR (126 MHz, DMSO-\(D_6\)) \(\delta\) 156.04, 155.74, 147.82, 146.94, 141.18, 140.71, 138.55, 133.46, 129.97, 128.89, 128.58, 128.18, 127.72, 127.30, 126.98, 126.76, 126.43, 126.34, 121.31, 120.42, 115.35, 115.28, 55.69, 55.67, 40.05, 21.80.

8 - (E)-(3,5-difluorostyryl)phosphonic acid
Synthesis followed microwave PA synthesis procedure above utilizing 3,5-difluorobromobenzene as the aromatic halide, this compound has been previously synthesized and reported\(^1\,^2\) and the \(^1\)H NMR (Figure S11) and HRMS (Table S1) characterization matches appropriately.
\(^1\)H NMR (500 MHz, DMSO-\(d_6\)) \(\delta\) 7.42 – 7.33 (m, 2H), 7.20 – 7.16 (m, 1H), 7.11 (dd, \(J = 20.2\) Hz, 1H), 6.63 (dd, \(J = 16.5\) Hz, 1H).

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Selected NMR of Synthesized products

Figure S1 - $^1$H NMR of CF3PA- (E)-(4-(trifluoromethyl)styryl)phosphonic acid (3)

Figure S2 – $^1$H NMR of (E)-(3,5-difluoro-4-(trifluoromethyl)styryl)phosphonic acid (4)
Figure S3 – $^{13}$C NMR of (E)-(3,5-difluoro-4-(trifluoromethyl)styryl)phosphonic acid (4)

$^{31}$P NMR (292 MHz, DMSO-d$_6$) δ 11.85.

Figure S4 – $^{31}$P NMR of (E)-(3,5-difluoro-4-(trifluoromethyl)styryl)phosphonic acid (4)
Figure S5 – $^{19}$F NMR of (E)-(3,5-difluoro-4-(trifluoromethyl)styryl)phosphonic acid (4)

Figure S6 – $^1$H NMR of (E)-(2,6-difluorostyryl)phosphonic acid (5)
Figure S7 – ¹H NMR of (E)-(4-methoxystyryl)phosphonic acid (6)

H NMR (300 MHz, DMSO-d₆): δ 7.15 – 6.98 (m, 2H), 6.87 – 6.84 (m, 4H), 6.79 (d, J = 14.0 Hz, 4H), 6.69 (d, J = 17.2 Hz, 2H), 6.27 – 6.07 (m, 1H), 3.71 – 3.63 (m, 8H).

Figure S8 – ¹H NMR of (E)-(4-(bis(4-methoxyphenyl)amino)styryl)phosphonic acid (7)

H NMR (300 MHz, DMSO-d₆): δ 7.96 (d, J = 8.9 Hz, 2H), 7.09 (d, J = 21.9, 17.4 Hz, 1H), 6.91 (d, J = 8.9 Hz, 2H), 6.27 (t, J = 18.9 Hz, 3H), 3.74 (s, 3H).
Figure S9 – $^{13}$C NMR of (E)-(4-(bis(4-methoxyphenyl)amino)styryl)phosphonic acid (7)

Figure S10 – Two dimensional heteronuclear correlation (HETCOR) of (E)-(4-(bis(4-methoxyphenyl)amino)styryl)phosphonic acid (7)
Figure S11 – $^1$H NMR of (E)-(3,5-difluorostyryl)phosphonic acid (8)

References