Heck Arylation of Styrenes Promoted by an Air-Stable Phosphinito Complex with Palladium(II); Synthesis of Resveratrol

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Abstract: An air-stable phosphinito complex of palladium(II) was found to be an efficient catalyst in the Heck reaction of a variety of aryl halides and styrenes. Resveratrol was concisely synthesized in 63% overall yield; the reactions were performed under conventional and microwave heating.

Key words: Heck reaction, palladium, homogeneous catalysis, halides, coupling

In recent years, derivatives of stilbenes have attracted attention because of their wide range of biological activity and potential therapeutic value.[1] Resveratrol (*trans*-3,4′,5-trihydroxystilbene, Figure 1) is perhaps the most recognized polyhydroxylated stilbene (naturally occurring), as it is easily found in vine bark, leaves, grapes, and other plants.[2] Resveratrol is usually synthesized in grapes in response to microbial infections or stress. However, it is also produced after exposure to chemical treatments, such as herbicide or fungicide application, and by UV light.[3] Recently, resveratrol has been thought to be the causative agent involved in the 'French paradox' and the molecule most responsible for the Mediterranean diet effect in which high fat intake coupled with moderate wine consumption leads to abnormally low rates of heart disease and cancer.[4] The use of resveratrol has also been implicated in the treatment of heart disease,[5] Alzheimer's disease,[6] platelet anti-aggregation,[7] cancer,[1b,e,8] and estrogenic activity,[9] as it acts as an anti-inflammatory[10] and antiviral agent.[11] Additionally, resveratrol has shown radical scavenging activity.[12] Interestingly, from the same family of stilbenes, Sale and co-workers have demonstrated the strong anti-cancer activity of DMU-212 (*trans*-3,4,4′,5-tetramethoxystilbene).

Carbon–carbon double bond formation is the key step in the synthesis of (*Z*)- and (*E*)-stilbenes.[13] Principal methods for the syntheses of these bonds involve the Wittig reaction[12c,14,15] for the *Z*-isomer and the Wittig–Horner reaction[14a,d,16] for the *E*-isomer. Other strategies used in the synthesis of stilbenes involve palladium-catalyzed Heck[17] and Suzuki[18] coupling reactions. Additionally, ruthenium-catalyzed cross-metathesis,[19] the Perkin reaction,[20] Diels–Alder/Wittig reaction,[21] Ramberg–Bäcklund reaction,[22] and lithiation condensation[23] have been used.

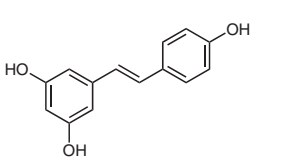

Figure 1 Resveratrol

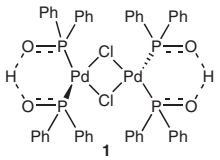

Figure 2 Phosphinito complex of palladium(II)

In this article, we wish to enrich this diverse range of strategies for stilbene synthesis using an air-stable phosphinito complex of palladium(II) **1** (Figure 2). As part of our interest in the preparation and application of this complex, we have recently demonstrated that complex **1** is useful in the Heck coupling of aryl halides with primary and secondary allylic alcohols[24] and in the Heck arylation of electron-deficient and electron-rich alkenes.[25] Complex **1** was first synthesized by Dixon in 1971,[26] and then later, the crystalline structure was reported by several groups[27] and used in the methoxycarbonylation of iodobenzene and in the cross-coupling of bromobenzene with butyl acrylate.[28] Similar platinum and palladium compounds containing hydrogen-bonded P–O–H–O–P ligands have also been prepared, and they have been used in the syntheses of amides and for the hydrophosphinylation of alkynes.

With this background, we channeled our efforts to demonstrate that complex **1** (Figure 2) can be useful in the palladium-catalyzed, highly chemo-, regio-, and stereoselective synthesis of *trans*-stilbene derivatives. Thus, we studied the use of **1** in the Heck reaction between iodobenzene (**2a**) and styrene (**3**) and compared its performance under standard and microwave conditions. After evaluating several solvent systems, we identified acetonitrile as the best solvent (Table 1, entries 7–9). Additionally, 1.0 mol% of **1** was sufficient to obtain a quantitative yield of *trans*-stilbene (**4a**) in 12 hours. Unfortunately, further attempts to decrease the amount of **1** to 0.1 or 0.01 mol% was reflected in lower yields (entries 10 and 11). Furthermore, the yield was lower still when sodium acetate was used as the base (entries 1, 4, and 7). Notably, in both pro-

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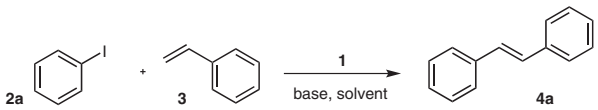
Table 1 Heck Reaction between Iodobenzene and Styrene[a]



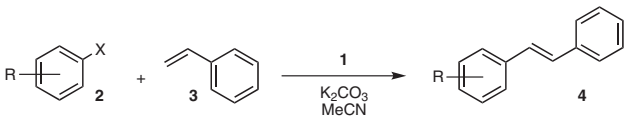
Entry	**1** (mol%)	Base	Solvent	Yield[b] (%)	
				A[c]	B[d]
1	1	NaOAc	toluene	20	22
2	1	Et_3N	toluene	85	87
3	1	K_2CO_3	toluene	85	90
4	1	NaOAc	DMF	20	25
5	1	Et_3N	DMF	76	80
6	1	K_2CO_3	DMF	78	80
7	1	NaOAc	MeCN	32	38
8	1	Et_3N	MeCN	90	95
9	1	K_2CO_3	MeCN	90	95
10	0.1	K_2CO_3	MeCN	70	70
11	0.01	K_2CO_3	MeCN	55	57

[a] Reaction conditions: **2a** (1 mmol), **3** (1.2 mmol), base (2 mmol).
[b] Yield of isolated product after chromatographic purification.
[c] Conventional heating 80 °C under argon, 12 h.
[d] Microwave heating 200 °C, 20 min.

cedures, under standard and microwave conditions, the *E*-isomer was observed as the sole product. Interestingly, complex **1** is also known to be stable for up to two years when stored at room temperature without any special conditions. ^{31}P NMR also showed that the complex was stable in the presence of water or methanol for five or ten hours, respectively. However, when the reactions were performed with styrene, it was necessary to use an argon atmosphere to avoid styrene polymerization.

Using the optimized reaction conditions, we next examined the application of **1** for the cross-coupling of a variety of aryl halides **2** and styrene (**3**) under 1.0 mol% catalyst loading (Table 2). The results indicate that **1** constituted a simple, yet efficient catalyst system for the Heck reactions of aryl halides. Both electron-rich (entries 1–4) and electron-poor (entries 5, 7, and 8) aryl iodides and bromides were efficiently converted into the desired products **4b–e** in high yields. However, when the reaction was carried out with aryl chlorides, the desired products were not observed (entries 6 and 9). The reaction is compatible with a variety of functional groups and gives the corresponding products **4f–h** with excellent yields (entries 10–12). Additionally, when the reactions were performed using a microwave irradiation conditions, the yields obtained were comparable to the thermal results, but they required shorter reaction times (Table 2). However, when the reaction was performed with 2- and 3-bromopyridines, complex **1** was active only with 3-bromopyridine (entry 14).

Table 2 Scope of the Palladium-Catalyzed Aryl Halide Heck Reaction[a]



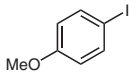
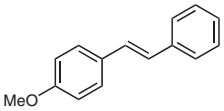
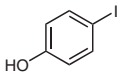
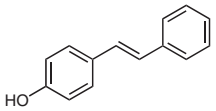
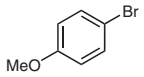
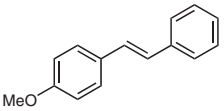
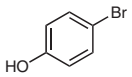
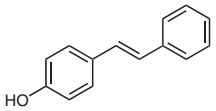
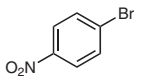
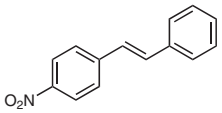
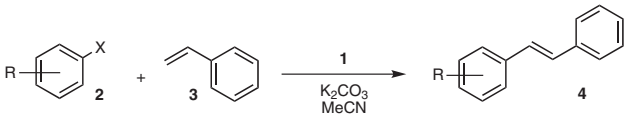
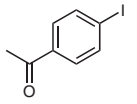
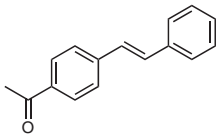
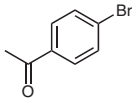
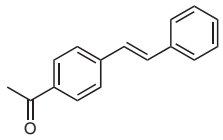
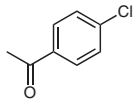
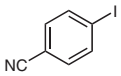
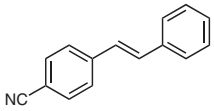
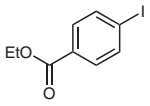
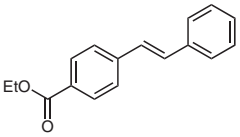
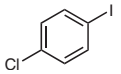
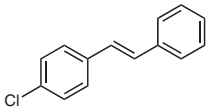
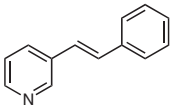
Entry	Ar-X		Stilbene		Yield[b] (%)	
					A[c]	B[d]
1	**2b**		**4b**		85	88
2	**2c**		**4c**		86	89
3	**2d**		**4b**		75	80
4	**2e**		**4c**		77	82
5	**2f**		**4d**		90	95

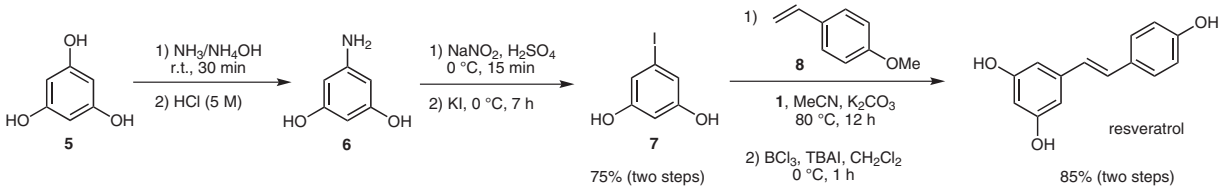
Table 2 Scope of the Palladium-Catalyzed Aryl Halide Heck Reaction[a] (continued)



Entry	Ar-X		Stilbene		Yield[b] (%)	
					A[c]	B[d]
6	**2g**		–		–	–
7	**2h**		**4e**		90	95
8	**2i**		**4e**		87	95
9	**2j**		–		–	–
10	**2k**		**4f**		90	95
11	**2l**		**4g**		90	95
12	**2m**		**4h**		88	90
14	**2n**		**4i**		90	95

[a] Reaction conditions: **2** (1 mmol), **3** (1.2 mmol), **1** (1 mol%), K_2CO_3 (2 mmol).
[b] Yield of isolated product after chromatographic purification.
[c] Conventional heating 80 °C under argon, 12 h.
[d] Microwave heating 200 °C, 20 min.

To illustrate the potential and efficiency of the described methodology, a concise synthesis of resveratrol was performed. As shown in Scheme 1, treatment of commercial phloroglucinol (**6**) with ammonia/ammonium hydroxide,[29] followed by Sandmeyer reaction,[30] provided iododiphenol **7** (75% yield). Next, the cross-coupling reaction between iododiphenol **7** and methoxystyrene **8** was performed. This reaction took place under standard thermal and microwave conditions using triethylamine, sodium acetate, or potassium carbonate as the base, and the solvent used was either toluene or acetonitrile. As shown in Table 3 (entry 6), a higher yield of resveratrol was obtained when the reaction was performed in the presence of potassium carbonate, using toluene as solvent and microwave heating (85%) after demethylation[31] with the boron trichloride/tetrabutylammonium iodide. However, when the reaction was performed with sodium acetate as the base, only the starting material was recovered (entries 1 and 4), and with a longer reaction time, decomposition was observed in the crude reaction mixture. Furthermore, similar yields were obtained when the Heck reaction was performed using the microwave conditions and shorter reaction times (see Table 3). Finally, with these results in hand, we can affirm that this procedure provides an efficient access to resveratrol with full regioselectivity, with-



Scheme 1 Synthesis of resveratrol

Table 3 Heck Reaction between Iododiphenol **7** and Styrene **8** To Give Resveratrol[a]

Entry	Base	Solvent	Yield[b] (%)	
			A[c]	B[d]
1	NaOAc	toluene	–	–
2	Et_3N	toluene	50	60
3	K_2CO_3	toluene	60	62
4	NaOAc	MeCN	–	–
5	Et_3N	MeCN	60	80
6	K_2CO_3	MeCN	75	85

[a] Reaction conditions: **7** (1 mmol), **8** (1.2 mmol), **1** (1 mol%), base (2 mmol).
[b] Yield of isolated product after elimination of the protecting group and chromatographic purification.
[c] Conventional heating 80 °C under argon, 12 h.
[d] Microwave heating 200 °C, 20 min.

out the use protecting groups in the aryl halide **7**, which is an important advantage in organic synthesis.

In conclusion, we have demonstrated that complex **1** is a highly efficient catalyst in chemo-, regio-, and stereoselective syntheses of stilbenes. Moreover, our synthetic approach afforded resveratrol in three steps in 63% overall yield. Finally, in all the examples, the use of microwave irradiation reduced the reaction time significantly. Therefore, we believe that this methodology will be of use for the efficient preparation of polymethoxylated stilbenes of biological interest.

All chemicals were purchased from Aldrich Chemical Co and used without further purification unless stated otherwise. Yields refer to the chromatographically and spectroscopically (^{1}H and ^{13}C) homogeneous materials, unless otherwise stated. All glassware utilized was flame-dried before use. Reactions were monitored by TLC carried out on 0.25-mm Macherey Nagel silica gel plates. Developed TLC plates were visualized under a short-wave UV lamp and by heating plates that were dipped in $Ce(SO_4)_2$. Flash column chromatography was performed using flash silica gel (230–400 mesh) and employed a solvent polarity correlated with TLC mobility. Microwave reactions were performed in an Anton Paar Monowave 300 in sealed reaction vessels. NMR experiments were conducted on Bruker-Avance 300 MHz instruments using $CDCl_3$ (99.9% D) as the solvent referenced to internal standards $CHCl_3$ (^{1}H, δ = 7.26 ppm; ^{13}C, δ = 77.0 ppm) or TMS as an internal reference (δ = 0.00 ppm).

Dipalladium Complex 1

A soln of Ph_2PCl (0.75 mL, 4.05 mmol) in THF (5 mL) was added dropwise with stirring to a Schlenk flask containing a soln of $[PdCl_2(PhCN)_2]$ (0.76 g, 2.0 mmol) in THF (10 mL) at r.t. When the complete formation of the dichlorophosphane complex had been confirmed by ^{31}P NMR spectroscopy (δ = 87 ppm), H_2O (0.5 mL) was added to the mixture and it was stirred at r.t. After 48 h, ^{31}P NMR analysis of an aliquot exclusively showed one signal at δ = 78.6 ppm. The solvent was removed under vacuum to give the complex **1** (1 g, 92%) as a yellow crystalline powder; mp 113–116 °C.

IR: 3441 (m) (O–H–O), 1435 (Ph), 1479 (w), 1023 cm^{-1} (m) (P–O).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.2–7.7 (Ph).

^{31}P NMR (121.4 MHz, $CDCl_3$): δ = 78.6.

Method A: Catalytic Reaction

In all Heck reactions, aryl halide (1 mmol), styrene (1.0 mmol), base (2 mmol), and catalyst **1** (1 mol%) in MeCN (3 mL) was heated in a 80 °C oil bath equipped with a condenser system for 12 h. When the reaction was complete, the mixture was cooled to r.t., diluted with EtOAc (15 mL), washed with brine (10 × 3 mL), dried (Na_2SO_4), and concentrated under vacuum. The resulting residue was purified via flash column chromatography (silica gel, 25 × 2.5 cm, EtOAc–hexane, 30:70).

Method B: Microwave Reaction

Sealed vessels containing the mixture were placed in an Anton Paar Monowave 300 system heated at 200 °C/27 bars for 20 min.

***trans*-Stilbene (4a)[32,33]**

Following the general procedure, the Heck reactions were carried out with **2a** (200 mg, 0.980 mmol), **3** (122 mg, 1.176 mmol), K_2CO_3 (270 mg, 1.961 mmol), and catalyst **1** (10 mg, 1 mol%). Yield: 159 mg (90%, method A), 168 mg (95%, method B).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.11 (s, 2 H), 7.23–7.27 (m, 2 H), 7.36 (t, *J* = 7.5 Hz, 4 H), 7.51 (d, *J* = 7.7 Hz, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 126.7, 127.8, 128.8, 128.9, 137.5.

Anal. Calcd for $C_{14}H_{12}$: C, 93.29; H, 6.71. Found: C, 93.22; H, 6.69.

***trans*-4-Methoxystilbene (4b)[32,33]**

Following the general procedure, the Heck reactions were carried out with **2b** (200 mg, 0.855 mmol), **3** (107 mg, 1.026 mmol), K_2CO_3 (236 mg, 1.709 mmol), and catalyst **1** (9 mg, 1 mol%). Yield: 153 mg (85%, method A), 158 mg (88%, method B).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.83 (s, 3 H), 6.90 (d, *J* = 8.7 Hz, 2 H), 6.98 (d, *J* = 16.4 Hz, 1 H), 7.08 (d, *J* = 16.4 Hz, 1 H), 7.23 (t, *J* = 7.0 Hz, 1 H), 7.34 (t, *J* = 7.5 Hz, 2 H), 7.44–7.50 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.5, 114.3, 126.4, 126.8, 127.3, 127.9, 128.4, 128.8, 130.3, 137.8, 159.5.

Anal. Calcd for $C_{15}H_{14}O$: C, 85.68; H, 6.71. Found: C, 85.61; H, 6.68.

***trans*-4-Hydroxystilbene (4c)[32,33]**

Following the general procedure, the Heck reactions were carried out with **2c** (200 mg, 0.909 mmol), **3** (113 mg, 1.091 mmol), K_2CO_3

(251 mg, 1.818 mmol), and catalyst **1** (10 mg, 1 mol%). Yield: 153 mg (86%, method A), 159 mg (89%, method B).

^{1}H NMR (300 MHz, acetone-d_6): δ = 6.85 (d, *J* = 7.7 Hz, 2 H), 7.05 (d, *J* = 16.4 Hz, 1 H), 7.16 (d, *J* = 16.4 Hz, 1 H), 7.19–7.21 (m, 1 H), 7.34 (t, *J* = 7.6 Hz, 2 H), 7.45 (d, *J* = 7.8 Hz, 2 H), 7.55 (d, *J* = 7.9 Hz, 2 H), 8.44 (s, 1 H).

^{13}C NMR (75 MHz, acetone-d_6): δ = 116.5, 126.5, 127.0, 127.8, 128.8, 129.4, 129.5, 130.0, 138.9, 158.3.

Anal. Calcd for $C_{14}H_{12}O$: C, 85.68; H, 6.16. Found: C, 85.65; H, 6.12.

trans-4-Nitrostilbene (4d)[32,33]

Following the general procedure, the Heck reactions were carried out with **2f** (200 mg, 0.990 mmol), **3** (124 mg, 1.188 mmol), K_2CO_3 (273 mg, 1.980 mmol), and catalyst **1** (11 mg, 1 mol%). Yield: 200 mg (90%, method A), 212 mg (95%, method B).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.14 (d, *J* = 16.5 Hz, 1 H), 7.27 (d, *J* = 16.5 Hz, 1 H), 7.33–7.43 (m, 3 H), 7.55 (d, *J* = 7.8 Hz, 2 H), 7.64 (d, *J* = 8.8 Hz, 2 H), 8.22 (d, *J* = 8.8 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 124.3, 126.5, 127.0, 129.0, 129.1, 133.5, 136.4, 144.0, 147.0.

Anal. Calcd for $C_{14}H_{11}NO_2$: C, 74.65; H, 4.92; N, 6.22. Found: C, 74.60; H, 4.88; N, 6.20.

trans-4-Acetylstilbene (4e)[32,33]

Following the general procedure, the Heck reactions were carried out with **2h** (200 mg, 0.813 mmol), **3** (101 mg, 0.976 mmol), K_2CO_3 (224 mg, 1.626 mmol), and catalyst **1** (9 mg, 1 mol%). Yield: 157 mg (87%, method A), 171 mg (95%, method B).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.61 (s, 3 H), 7.14 (d, *J* = 16.4 Hz, 1 H), 7.22 (d, *J* = 16.4 Hz, 1 H), 7.25–7.38 (m, 3 H), 7.55 (d, *J* = 7.9 Hz, 2 H), 7.59 (d, *J* = 8.4 Hz, 2 H), 7.95 (d, *J* = 8.4 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.7, 126.6, 126.9, 127.6, 128.4, 128.9, 129.0, 131.6, 136.1, 136.8, 142.1, 197.6.

Anal. Calcd for $C_{16}H_{14}O$: C, 86.45; H, 6.35. Found: C, 86.42; H, 6.32.

trans-4-Cyanostilbene (4f)[32,33]

Following the general procedure, the Heck reactions were carried out with **2k** (200 mg, 0.873 mmol), **3** (109 mg, 1.048 mmol), K_2CO_3 (241 mg, 1.747 mmol), and catalyst **1** (9 mg, 1 mol%). Yield: 161 mg (90%, method A), 170 mg (95%, method B).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.08 (d, *J* = 6.4Hz, 1 H), 7.20 (d, *J* = 16.3 Hz, 1 H), 7.31–7.40 (m, 3 H), 7.51–7.64 (m, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 110.6, 119.1, 126.8, 126.9, 127.0, 128.7, 128.9, 132.5, 132.5, 136.4, 141.9.

Anal. Calcd for $C_{15}H_{11}N$: C, 87.77; H, 5.40; N, 6.82. Found: C, 87.73; H, 5.36; N, 6.80.

Ethyl *trans*-Stilbene-4-carboxylate (4g)[32,33]

Following the general procedure, the Heck reactions were carried out with **2l** (200 mg, 0.725 mmol), **3** (90 mg, 0.870 mmol), K_2CO_3 (200 mg, 1.449 mmol), and catalyst **1** (8 mg, 1 mol%). Yield: 164 mg (90%, method A), 173 mg (95%, method B).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.41 (t, *J* = 7.2 Hz, 3 H), 4.39 (q, *J* = 7.2 Hz, 2 H), 7.12 (d, *J* = 16.2 Hz, 1 H), 7.23 (d, *J* = 16.2 Hz, 1 H,), 7.29–7.33 (m, 1 H), 7.34–7.43 (m, 2 H), 7.53–7.59 (m, 4 H), 8.03 (d, *J* = 8.4 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.8, 60.9, 126.2, 126.7, 127.6, 128.2, 128.7, 129.3, 129.9, 131.1, 136.7, 141.7, 166.3.

Anal. Calcd for $C_{17}H_{16}O_2$: C, 80.93; H, 6.39. Found: C, 80.89; H, 6.35.

trans-4-Chlorostilbene (4h)[32,33]

Following the general procedure, the Heck reactions were carried out with **2m** (200 mg, 0.840 mmol), **3** (105 mg, 1.008 mmol), K_2CO_3 (232 mg, 1.681 mmol), and catalyst **1** (9 mg, 1 mol%). Yield: 158 mg (88%, method A), 162 mg (90%, method B).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.07 (s, 2 H), 7.26–7.41 (m, 5 H), 7.44 (d, *J* = 8.8 Hz, 2 H), 7.50 (d, *J* = 7.4 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 126.5, 127.3, 127.6, 127.8, 128.7, 128.8, 129.3, 133.1, 135.8, 136.9.

Anal. Calcd for $C_{14}H_{11}Cl$: C, 78.32; H, 5.16. Found: C, 78.29; H, 5.12.

trans-3-Styrylpyridine (4i)[32,33]

Following the general procedure, the Heck reactions were carried out with **2n** (200 mg, 1.266 mmol), **3** (158 mg, 1.519 mmol), K_2CO_3 (349 mg, 2.532 mmol), and catalyst **1** (14 mg, 1 mol%). Yield: 206 mg (90%, method A), 218 mg (95%, method B).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.06 (d, *J* = 16.4 Hz, 1 H), 7.16 (d, *J* = 16.3 Hz, 1 H), 7.26–7.40 (m, 4 H), 7.53 (m, 2 H), 7.85 (d, *J* = 9.0 Hz, 1 H), 8.48 (m, 1 H), 8.72 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 123.5, 124.9, 126.7, 128.2, 128.4, 128.8, 130.8, 132.6, 133.0, 136.7, 148.6.

Anal. Calcd for $C_{13}H_{11}N$: C, 86.15; H, 6.12; N, 7.73. Found: C, 86.12; H, 6.09; N, 7.70.

5-Iodobenzene-1,3-diol (7)[30]

Concd NH_4OH (30 mL) was added to phloroglucinol (5 g, 39.68 mmol) at 0 °C. Upon completion of the addition a stream of NH_3 was bubbled into the mixture for 60 min. The cooling bath was removed and stirring was continued at r.t. for 72 h. Vacuum concentration of the clear brown soln gave a solid, to which was added 5 M HCl (20 mL), and the mixture was concentrated under vacuum to afford a yellow solid. This solid was used directly in the next step.

To an ice-salt cooled soln of 5-aminoresorcinol hydrochloride (4 g, 24.84 mmol) in H_2O (50 mL) was added concd H_2SO_4 (5 mL). After addition of a soln of $NaNO_2$ (4.85 g, 69.8 mmol) in H_2O (20 mL), the mixture was stirred for 15 min at 0 °C and then EtOAc (25 mL) was added. A soln of KI (15 g, 90 mmol) in H_2O (15 mL) was added slowly to control the evolution of N_2. After 7 h, the layers were separated, and the aqueous layer was extracted with additional EtOAc (3 × 30 mL). The organic layers were washed with 25% $Na_2S_2O_3$ soln (3 × 25 mL), 1 M HCl (3 × 25 mL), and brine (3 × 25 mL), then dried ($MgSO_4$), filtered, and concentrated to a brown oil. The crude mixture was purified by chromatography (silica gel, gradient EtOAc–hexane) to yield **7** (4.3 g, 75%) as a white solid.

^{1}H NMR (300 MHz, acetone-d_6): δ = 6.72 (s, 1 H), 6.33 (s, 2 H), 8.40 (br s, 2 OH),

^{13}C NMR (75 MHz, acetone-d_6): δ = 93.8, 106.8, 116.3, 159.3.

Anal. Calcd for $C_6H_5IO_2$: C, 30.53; H, 2.14. Found: C, 30.50; H, 2.12.

Resveratrol[17]

Following the general procedure, the Heck reactions was carried out with 5-iodobenzene-1,3-diol (**7**, 100 mg, 0.423 mmol), **8** (68 mg, 0.508 mmol), K_2CO_3 (116 mg, 0.846 mmol), and catalyst **1** (4 mg, 1 mmol%). The crude product was used directly in the next step.

To the mixture of the crude product and TBAI (936 mg, 2.538 mmol) in anhyd CH_2Cl_2 (4 mL), 1 M BCl_3 in CH_2Cl_2 (2.5 mL) was added dropwise at 0 °C under an argon atmosphere. Stirring was continued for 7 h, while the mixture was allowed to warm to r.t. Then, sat. aq $NaHCO_3$ (5 mL) was added dropwise at 0 °C and the resulting suspension stirred for 1 h at r.t., followed by extraction with EtOAc (3 × 15 mL). The organic phases were combined, dried

($MgSO_4$), and filtered. The solvent was removed under reduced pressure and the product was purified by flash chromatography (silica gel, gradient EtOAc–hexane) to yield resveratrol as a white solid [method A: 72 mg (75%); method B: 81 mg (85%)].

^{1}H NMR (300 MHz, acetone-d_6): δ = 7.39 (d, *J* = 8.1 Hz, 2 H), 6.98 (d, *J* = 16.2 Hz, 1 H), 6.87 (d, *J* = 16.2 Hz, 1 H), 6.82 (d, *J* = 8.1 Hz, 2 H), 6.52 (d, *J* = 2.2 Hz, 2 H), 6.24 (t, *J* = 2.1 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.3, 158.1, 140.6, 129.8, 128.9, 128.5, 126.6, 116.2, 105.5, 102.5.

Anal. Calcd for $C_{14}H_{12}O_3$: C, 73.67; H, 5.30. Found: C, 73.63; H, 5.28.

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