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Synthesis of methylated resveratrol and analogues by Heck reactions in organic and aqueous solvents

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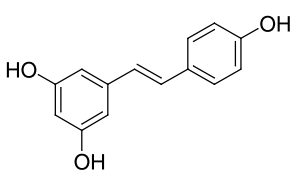
Dedicated to Professor José Luis Soto on occasion of his retirement

Abstract—The Heck reaction under phosphane free conditions using oxime-derived palladacycles or $Pd(OAc)_2$ as catalysts is a general methodology for the synthesis of methoxylated (*E*)-stilbene derivatives. Couplings can be performed either with (dicyclohexyl)methylamine as base and TBAB in aqueous DMA or in neat water and with Et_3N as base in DMA in air and under thermal and microwave conditions. The arylation of different styrenes are performed with 3,5-dimethoxyiodobenzene to afford a series of important biologically active (*E*)-stilbene derivatives containing the 3,5-dimethoxyphenyl moiety, including resveratrol, piceatannol and pinosilvine, which are efficiently prepared with high regioselectivity and total stereoselectivity (TON up to 10^4).

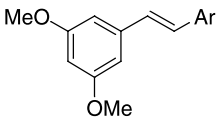
1. Introduction

Hydroxylated (*E*)-stilbenoids are natural polyphenols widely present in nature, especially in medicinal plants and food products,[1] which exhibit a variety of biological and therapeutical properties.[2–15] The phytoalexin resveratrol (**1**, Fig. 1), 3,4′,5-trihydroxy-(E)-stilbene, the biosynthetic precursor of most oligostilbenoids became the most famous compound as it was suggested as cancer chemopreventive agent[2] and due to its antiinflamatory[3] and antioxidative[4] properties may contribute also as chemoprotective agent.[5] In addition, it presents in vitro growth inhibition in a number of human cancer cell lines.[6] Resveratrol also prevents heart diseases due to lipid-lowering-activity and lipid peroxidation-inhibition.[7–9] Other properties, such as radical scavenging activity,[10] neuroprotection,[11] antiviral activity[12] and to promote survival and longevity by activating siruins[13] have also been recently found. For all these reasons new resveratrol analogues have been designed as chemotherapeutic agents.[14–16] For instance, the trimethyl ether of resveratrol **2a** shows more activity against several human cancer cell lines than resveratrol (**1**)[14] and methoxylated stilbenes, such as **2b** and **2c** are potent CYP1B1 inhibitors valuable for the development of a chemopreventive or therapeutic agent for cancer[16] (Fig. 1). Therefore, the development of general and simple strategies for the preparation of methoxylated stilbenoids for biological evaluation has became an important task.

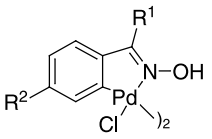
Several synthetic routes are based mainly on: (a) Wittig-type[1f,14–17] and modified Julia[18] olefinations, (b) reaction of 3,5-dimethoxybenzyllithium with 4-methoxybenzaldehyde followed by dehydration,[19] (c) Perkins reaction[20] (d) cross metathesis of styrenes,[21] (e) Suzuki reaction with β-halostyrenes,[22] (f) decarbonylative Heck reaction between resorcylic acid chloride and 4-acetoxystyrene,[23] (g)



1



2a: Ar = 4-$(MeO)C_6H_4$
2b: Ar = 2-thienyl
2c: Ar = 2,4-$(MeO)_2C_6H_3$



3a: R^1 = Me; R^2 = OH
3b: R^1 = 4-ClC_6H_4; R^2 = Cl

Figure 1.

Keywords: Resveratrol; Heck reaction; Palladacycles; Stilbenes; Styrenes.
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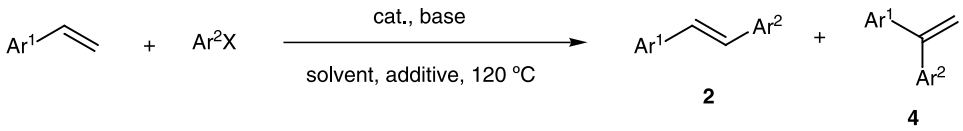


Scheme 1.

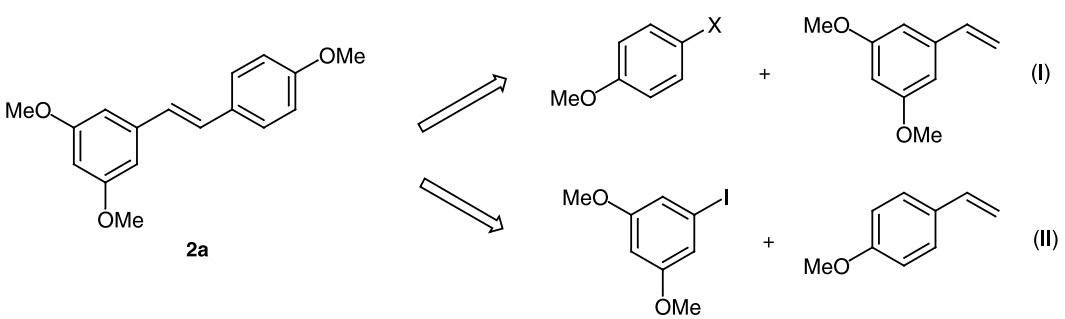
one-pot[24] sequential Heck arylation–desilylation of vinyltrimethylsilane followed by Heck arylation of styrene derivatives formed in situ and (h) by arylation of 3,5-dimethoxystyrene with 4-(benzyloxy)iodobenzene.[25] The main inconvenient for the palladium-catalyzed arylation of styrenes is the low reactivity of electron-rich styrenes and iodides.[26] Thus, the last two processes require the use of inert atmosphere and high loadings (2 mol%) of $Pd(dba)_2$[24] or the addition of silver nitrate at 120 °C during one week[25] to afford the corresponding resveratrol derivatives. As part of our project about the use of oxime-derived palladacycles **3** in C–C bond-forming reactions in organic[27] and aqueous media[28] we have focussed our attention on the possible applications of these catalysts for the synthesis of methoxylated stilbenes by Heck couplings of substituted aryl halides and styrenes.

2. Results and discussion

We first tested the arylation reaction of the rather reactive 4-chlorostyrene with activated 4-chlorophenyl and deactivated 4-methoxyphenyl iodides and bromides (Scheme 1 and Table 1) using 4-hydroxyacetophenone oxime-derived palladacycle **3a** as catalyst. However, under the reaction conditions established for arylation of acrylates,[28c] such as water reflux and (dicyclohexyl)methylamine as base the reaction was rather slow even with aryl iodides (Table 1, entries 1 and 4). When the process was performed in aqueous *N*,*N*-dimethylacetamide (DMA/H_2O: 4/1) at 120 °C (bath temperature) reaction times decreased, especially if 1 equiv of TBAB was added (Table 1, entries 2, 3 and 5, 6). For 4-chlorophenyl bromide the same effect was observed in aqueous DMA and TBAB as additive (Table 1, entries 7 and 8). Deactivated 4-methoxyphenyl bromide was coupled with 4-chlorostyrene under these conditions with palladacycle **3a** (0.5 mol% of Pd) in longer reaction times (1 d) and with $Pd(OAc)_2$[29] as catalyst only 2% conversion was observed (Table 1, entries 9 and 10). In all cases (*E*)-stilbene derivatives **2d** and **2e** with very low amounts of 1,1-diarylstyrenes **4** were observed and pure compounds **2** were isolated after flash chromatography.

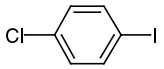
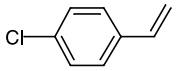
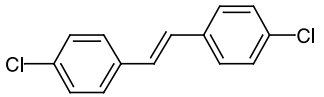
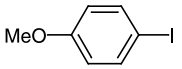
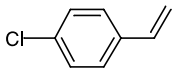
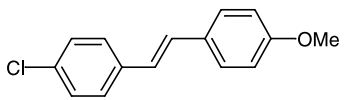
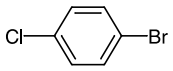
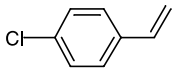
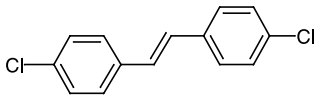
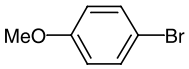
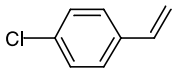
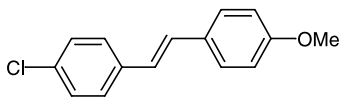
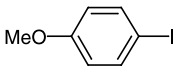
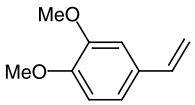
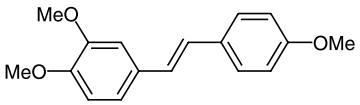
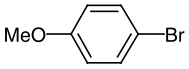
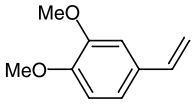
For subsequent studies between methoxylated partners commercially available 3,4-dimethoxystyrene and 4-methoxyiodobenzene were chosen as model substrates. For the couplings in aqueous DMA the presence of TBAB improved the efficiency of the catalyst **3a** (0.01 mol% Pd) (Table 1, entry 11) and Cy_2NMe as base gave better yields than Et_3N (Table 1, compare entries 11 and 12). On the other hand, under these reaction conditions, $Pd(OAc)_2$ led to the same results as complex **3a** (Table 1, compare entries 11 and 13). Couplings performed in neat DMA took place in shorter times in the presence of Et_3N instead of Cy_2NMe as base (Table 1, compare entries 14 and 15). In this case both palladacycles **3** and $Pd(OAc)_2$ were employed as catalysts, the former being the most active source of Pd (Table 1, entries 15–17). However, the coupling under water reflux and with Cy_2NMe as base failed. When 3,4-dimethoxystyrene was arylated with 4-methoxybromobenzene in DMA/H_2O, Cy_2NMe as base and TBAB as additive the amount of **3a** has to be increased to 0.5 mol% Pd to afford high conversions in 19 h. However, $Pd(OAc)_2$ failed as catalyst under these conditions (Table 1, compare entries 18 and 19). For couplings in DMA the presence of TBAB was necessary either with Cy_2NMe or Et_3N as base (Table 1, entries 20–22) and both catalysts **3a** and $Pd(OAc)_2$ gave similar results (Table 1, compare entries 21 and 23). Finally this coupling was carried out under Jeffery's conditions, so in the presence of K_2CO_3 as base the reaction was slower than with organic amines and $Pd(OAc)_2$ gave slightly better yields than palladacycle **3a** (Table 1, entries 24 and 25). From these studies we deduced that for the couplings of methoxylated styrene and aryl halides two method can be used, Method A: DMAc/H_2O, Cy_2NMe as base and TBAB as additive and either catalyst **3a** or $Pd(OAc)_2$ as catalysts except for aryl bromides, which required the use of **3a** and Method B: DMAc and Cy_2NMe or Et_3N as base, the presence of TBAB being required in the case of aryl bromides as arylating components. The regioselectivity was lower with 3,4-dimethoxystyrene than with 4-chlorostyrene and higher with aryl bromides than iodides.

For the preparation of biologically active 3,5-dimethoxy-(*E*)-stilbenes the use of different, commercially available or prepared by Wittig reaction,[30] aryl and heteroarylethylenes



Scheme 2.

Table 1. Reaction conditions optimization for the Heck reaction[a]

Entry	ArX	Styrene	Cat. (mol% Pd)	Amine	Solvent	Additive	t (h)	Product	
								No.	Yield (%)[b]
1			**3a** (1.1×10^{-2})	Cy_2NMe	H_2O	—	30	**2d** 	96 [16:1] (79)
2			**3a** (10^{-2})	Cy_2NMe	DMA/H_2O	—	20	**2d**	99 [15:1]
3			**3a** (10^{-2})	Cy_2NMe	DMA/H_2O	TBAB	9	**2d**	99 [19:1]
4			**3a** (0.1)	Cy_2NMe	H_2O	—	72	**2e** 	89 [8.9:1] (75)
5			**3a** (0.1)	Cy_2NMe	DMA/H_2O	—	48	**2e**	86 [9.2:1]
6			**3a** (9.1×10^{-2})	Cy_2NMe	DMA/H_2O	TBAB	9	**2e**	99 [12:1]
7			**3a** (0.52)	Cy_2NMe	DMA/H_2O	—	38	**2d** 	99 [24:1] (89)
8			**3a** (10^{-2})	Cy_2NMe	DMA/H_2O	TBAB	15	**2d**	94 [25:1]
9			**3a** (0.5)	Cy_2NMe	DMA/H_2O	TBAB	24	**2e** 	87 [18:1] (81)
10			$Pd(OAc)_2$ (0.5)	Cy_2NMe	DMA/H_2O	TBAB	24	**2e**	2
11			**3a** (10^{-2})	Cy_2NMe	DMA/H_2O	TBAB	19	**2f** 	99 [5.7:1]
12			**3a** (10^{-2})	Et_3N	DMA/H_2O	TBAB	20	**2f**	43 [7.3:1]
13			$Pd(OAc)_2$ (1.5×10^{-2})	Cy_2NMe	DMA/H_2O	TBAB	19	**2f**	98 [6.1:1]
14			**3a** (10^{-2})	Cy_2NMe	DMA	—	24	**2f**	99 [4.9:1]
15			**3a** (1.1×10^{-2})	Et_3N	DMA	—	3.5	**2f**	95 [4.6:1]
16			**3b** (9.1×10^{-3})	Et_3N	DMA	—	6	**2f**	91 [4.4:1]
17			$Pd(OAc)_2$ (10^{-2})	Et_3N	DMA	—	3.5	**2f**	86 [4.6:1]
18			**3a** (0.5)	Cy_2NMe	DMA/H_2O	TBAB	19	**2f**	84 [9.2:1]
19			$Pd(OAc)_2$ (0.5)	Cy_2NMe	DMA/H_2O	TBAB	19	**2f**	0
20			**3a** (0.5)	Cy_2NMe	DMA	—	24	**2f**	75 [7:1]
21			**3a** (0.5)	Cy_2NMe	DMA	TBAB	3.5	**2f**	99 [10:1]
22			**3a** (0.5)	Et_3N	DMA	TBAB	3.5	**2f**	80 [11.3:1]
23			$Pd(OAc)_2$ (0.5)	Cy_2NMe	DMA	TBAB	3.5	**2f**	99 [14.3:1]
24			**3a** (0.5)	K_2CO_3	DMA	TBAB	7.5	**2f**	82 [10.3:1]
25			$Pd(OAc)_2$ (0.5)	K_2CO_3	DMA	TBAB	7.5	**2f**	99 [9.9:1]

[a] Reaction conditions: ArX (1 mmol), styrene (1.5 mmol), amine (1.5 mmol), TBAB (1 mmol), H_2O (3 mL) or DMA/H_2O (4/1, 5 mL) or DMA (3 mL), 120 °C (bath temperature), pressure tube. For 10^{-2} mol% Pd: ArX (2 mmol), styrene (3 mmol), amine (3 mmol), TBAB (2 mmol).

[b] Conversion determined by GC based on ArX using decane as an internal standard. In brackets, regioisomers ratio of crude product (determined by GC). In parenthesis, isolated yield of the (*E*)-stilbene after flash chromatography (hexane/EtOAc).

Table 2. Synthesis of methoxylated (*E*)-stilbene derivatives

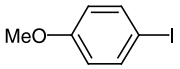
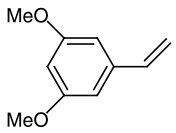
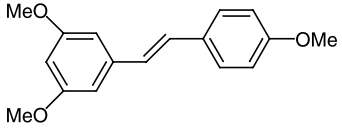
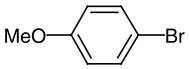
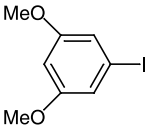
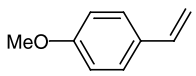
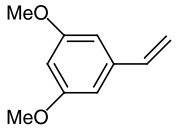
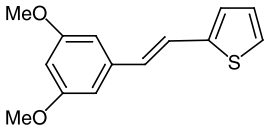
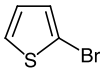
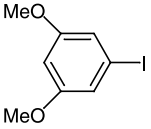
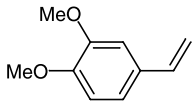
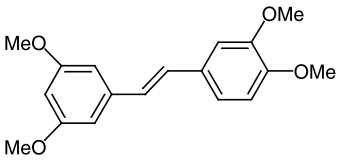
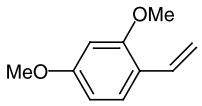
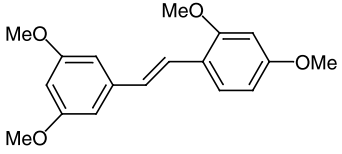
Entry	ArX	Styrene	Cat. (mol% Pd)	Reaction conditions[a]	*t*	Product	
						No.	Yield (%)[b]
1			**3a** (10^{-1})	Method A	14 h	**2a**	 99 [8.4:1] (77)
2			**3a** (1.1×10^{-2})	Method A	24 h	**2a**	77 [8:1]
3			$Pd(OAc)_2$ (1.1×10^{-2})	Method A	24 h	**2a**	88 [7.9:1]
4			**3a** (0.5)	Method A	14 h	**2a**	99 [10.5:1]
5			$Pd(OAc)_2$ (0.5)	Method A	14 h	**2a**	2
6			**3a** (0.5)	Method A[c]	10 min	**2a**	99 [6.3:1]
7			**3a** (1.1×10^{-2})	Method A	13 h	**2a**	96 [8.5:1] (85)
8			$Pd(OAc)_2$ (10^{-2})	Method A	13 h	**2a**	93 [10:1]
9			**3a** (10^{-2})	Method B	5 h	**2a**	95 [6:1]
10			$Pd(OAc)_2$ (10^{-2})	Method B	5 h	**2a**	99 [6.1:1]
11			**3a** (0.1)	Method C	23 h	**2a**	99 [9:1]
12			**3a** (0.15)	Method A	14 h	**2b**	 75 [14:1] (67)
13			**3a** (0.5)	Method A	8 h	**2b**	98 [16:1] (64)
14			**3a** (0.1)	Method A	14 h	**2c**	 98 [9.6:1] (75)
15			**3a** (0.1)	Method A	14 h	**2g**	 99 [4.2:1] (47)

Table 2 (*continued*)

Entry	ArX	Styrene	Cat. (mol% Pd)	Reaction conditions[a]	*t*	Product		
						No.		Yield (%)[b]
16			**3a** (0.1)	Method A	14 h	**2h**		99 [9.5:1] (86)
17			**3a** (0.1)	Method A	14 h	**2i**		99 [31:1] (94)

[a] Method A: DMA/H_2O (4/1), Cy_2NMe, TBAB, 120 °C (bath temperature). Method B: DMA, Et_3N, 120 °C (bath temperature). Method C: H_2O, Cy_2NMe, TBAB, 120 °C (bath temperature).

[b] Conversions determined by GC with decane as internal standard. In brackets, regioisomers ratio of crude product (determined by GC). In parenthesis, isolated yield of the (*E*)-stilbene **2** after flash chromatography (hexane/EtOAc).

[c] The reaction was performed under microwave irradiation conditions (120 W, 120 °C) at 0.5 mmol scale.

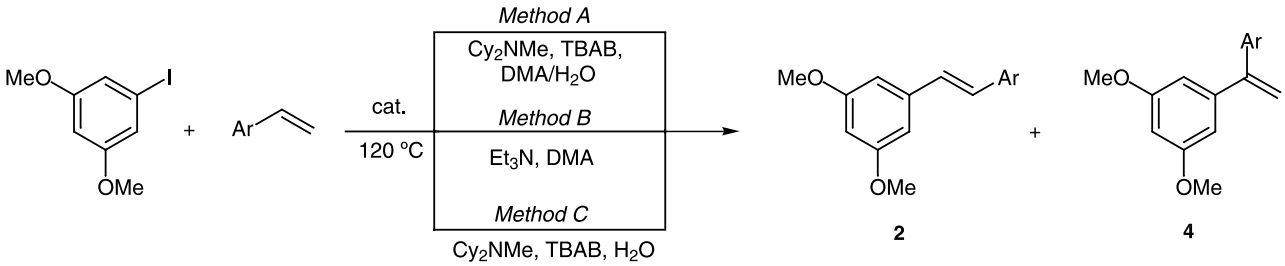
and 3,5-dimethoxyiodobenzene[31] as partners could be the most general strategy for combinatorial chemistry. However, for initial studies for methylated resveratrol (**2a**) two approaches were studied: (I) the arylation of 3,5-dimethoxystyrene[30,32] with 4-methoxyphenyl iodide and bromide and (II) the coupling of 4-methoxystyrene with 3,5-dimethoxyiodobenzene (Scheme 2 and Table 2). Both strategies gave good conversions when the reactions were performed following Method A–C (Table 2, entries 1–11) either under thermal or microwave conditions. There are some exceptions, such as using of $Pd(OAc)_2$ as catalyst the coupling of 4-methoxybromobenzene and 3,5-dimethoxystyrene failed (Table 2 entries 5) also under microwave conditions. The second strategy gave very low conversions under microwave conditions either with complex **3** or with $Pd(OAc)_2$ as catalysts.

Considering aryl iodides, strategy II occurred faster and with higher conversion than strategy I, it means that 3,5-dimethoxyiodobenzene is more reactive than 4-methoxyiodobenzene (Scheme 3, Table 2, compare entries 2 and 7 or 3 and 8). Following Method B (DMA, Et_3N) this second procedure occurred faster but with lower regioselectivity (Table 2, entries 9 and 10). Trimethylated resveratrol **2a** can also be prepared in water with (dicyclohexyl)methylamine as base and TBAB as additive (Method C) under thermal conditions although in longer reaction times than using Method A and B (Table 2, entry 11). However under microwave conditions the reaction took place with much lower conversion (20%). Conditions of Method A were used in the preparation of other methoxylated stilbenes because of the higher regioselectivity observed in the synthesis of resveratrol **2a**. In the case of stilbene **2b** 2-iodo and 2-bromothiophene were coupled efficiently with 3,5-dimethoxystyrene and with high regioselectivity (Table 2, entries 12 and 13, respectively).

For the rest of methoxylated stilbenes **2c**, **2g**–**2i**, 3,5-dimethoxyiodobenzene was coupled with the corresponding styrene (Scheme 3 and Table 2, entries 14–17). 2,4-Dimethoxystyrene[33] was prepared by Wittig reaction[30] and the rest of styrenes are commercially available. Compounds **2g** and **2i** along with **2a**–**c** present human cytochrome P450 1B1 inhibitory activity.[16] By demethylation of stilbenes **2a**, **2g** and **2h** by standard methods[19,24] natural products, such as resveratrol, piceatannol and pinosilvine, respectively can be obtained.

3. Conclusion

In conclusion, we have found appropriate reaction conditions to perform the Heck reaction between deactivated aryl halides and styrenes using oxime-derived palladacycle **3a** or $Pd(OAc)_2$ as catalysts in air and under phosphane and silver salt-free conditions. The reactions can be performed using (dicyclohexyl)methylamine in aqueous DMA or in neat water and TBAB as additive and in DMA with Et_3N as base. The former reaction conditions allowed the coupling between 3,5-dimethoxyiodobenzene and styrenes with the best regioselectivity. This methodology is an efficient regio and stereoselective way for the preparation of biologically active methoxylated stilbenes.



Scheme 3.

4. Experimental

4.1. General

All reagents and solvents were obtained from commercial sources and were generally used without further purification. Palladacycle **3** was purchased from MEDALCHEMY S. L. Microwave reactions were performed with a CEM Discover Synthesis Unit (CEM Corp., Matthews, NC) in glass vessels (10 mL) sealed with a septum under magnetic stirring. The catalysts were weighed out in an electronic microscale (Sartorius, XM1000P) with a precision of 1 μg. Thin liquid chromatography for R_f was performed on Polygram® Silica Gel 60 UV_{254} plates, purchased from Merck. Mp were measured in a Reichert Thermovar apparatus. Gas chromatographic analyses were performed on an HP-5890 instrument equipped with a WCOT HP-1 fused silica capillary column using decane as internal standard. IR data were collected on a Nicolet Impact 400D-FT. ^{1}H NMR spectra were recorded on a Bruker AC-300 MHz spectrometer and ^{13}C NMR spectra were recorded at 75 MHz with $CDCl_3$ as the internal reference. Mass spectra (MS) were obtained at 70 eV on a Hewlett Packard HP 6890 series GC system with a 5973 network mass selective detector.

4.2. Heck reactions. General procedures for the preparation of compound 2

Method A. A 15 mL Ace pressure tube was charged with aryl halide (1 mmol), styrene (1.5 mmol), (dicyclohexyl)-methylamine (0.32 mL, 1.5 mmol), tetrabutylammonium bromide (0.32 g, 1 mmol), catalyst (0.1–0.5 mol % Pd), DMA (4 mL) and water (1 mL). Reactions with 10^{-2} mol % Pd were performed at 2 mmol scale with the same amount of solvents. The solution was stirred at 120 °C in air and the reaction progress was analyzed by GC. After the reaction was completed or stopped, the reaction mixture was poured into ethyl acetate (20 mL) and washed with 2 M HCl (2×10 mL) and water (2×10 mL). The organic phase was dried over Na_2SO_4 and evaporated (15 Torr). The subsequent residue was purified by flash chromatography on silica gel to obtain the corresponding styrene. Only in the preparation of compound **2i**, the reaction mixture was poured into water (40 mL) and extracted with ethyl acetate (2×15 mL). The combined organic phases were washed with aqueous saturated $NaHCO_3$ solution (3×10 mL), dried over Na_2SO_4 and evaporated (15 Torr) to obtain a residue which was purified by flash column chromatography on silica gel.

Method B. A 15 mL Ace pressure tube was charged with aryl halide (2 mmol), styrene (3 mmol), triethylamine (0.42 mL, 3 mmol), catalyst (10^{-2} mol% Pd) and DMA (3 mL). The solution was stirred at 120 °C in air and the reaction progress was analyzed by GC. After the reaction was completed or stopped the same extractive work-up as before was performed.

Method C. A 15 mL Ace pressure tube was charged with aryl iodide (1 mmol), styrene (1.5 mmol), (dicyclohexyl)-methylamine (0.32 mL, 1.5 mmol), tetra-*n*-butylammonium bromide (0.32 mg, 1 mmol), **3a** (292 μg, 0.001 mmol Pd) and water (2 mL). The mixture was stirred at 120 °C in air and the reaction progress was analyzed by GC. After the reaction was completed or stopped, the same extractive work-up as before was performed.

All compounds have been previously reported and were characterized by comparison with their reported physical and spectroscopic data:

(*E*)-1-(3,5-Dimethoxyphenyl)-2-(4-methoxyphenyl)-ethene (**2a**). Mp 53–56 °C (lit.[16] 55–57 °C).
(*E*)-1-(3,5-Dimethoxyphenyl)-2-(2-thiophenyl)ethene (**2b**).[16] Oil.
(*E*)-1-(3,4-Dimethoxyphenyl)-2-(3,5-dimethoxyphenyl)-ethene (**2c**). Mp 67–68 °C (lit.[16] 66–67 °C).
(*E*)-1,2-Di(4-chlorophenyl)ethene (**2d**). Mp 175–178 °C (lit.[34] 177–178 °C).
(*E*)-1-(4-Chlorophenyl)-2-(4-methoxyphenyl)ethene (**2e**). Mp 181–184 °C (lit.[35] 185 °C).
(*E*)-1-(3,4-Dimethoxyphenyl)-2-(4-methoxyphenyl)-ethene (**2f**). Mp 136–138 °C (lit.[36] 133–135 °C).
(*E*)-1-(2,4-Dimethoxyphenyl)-2-(3,5-dimethoxyphenyl)-ethene (**2g**). Mp 82–83 °C (lit.[16] 78–79 °C).
(*E*)-1-(3,5-Dimethoxyphenyl)-2-phenylethene (**2h**). Mp 54–55 °C (lit.[37] 59–60 °C).
(*E*)-1-(3,5-Dimethoxyphenyl)-2-(4-pyridyl)ethene (**2i**). Mp 69–70[38] (lit.[16] 139–144 °C).

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