



One-pot palladium-catalyzed highly chemo-, regio-, and stereoselective synthesis of *trans*-stilbene derivatives. A concise and convenient synthesis of resveratrol

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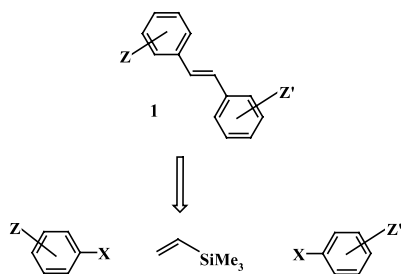
Abstract—A convenient, efficient and highly chemo-, regio-, and stereoselective one-flask synthetic method is reported for the construction of unsymmetrical (or symmetrical) *trans*-stilbene derivatives based on two sequential Heck-type reactions using tetraalkylammonium salt-based catalyst systems and vinyltrimethylsilane as double bond equivalent. Resveratrol has thus been concisely synthesized. © 2002 Elsevier Science Ltd. All rights reserved.

Many stilbene compounds **1** which are widely encountered in nature are known to have important biological activities.¹ Additionally, the importance of π -conjugated oligomers with the *p*-phenylenevinylene (PPV) backbone in the field of electroluminescent and non-linear optical (NLO) materials has been highlighted.² The double bond of the stilbene unit is usually elaborated from substituted benzaldehydes via Wittig^{1b,3a,c,e,f} or Horner–Wadsworth–Emmons reactions.^{1c,3a,b,d,f} Alternatively, construction of the stilbene structural unit from a preexisting double bond via arylation of styrene derivatives (Heck reaction) has been described.⁴ The combined use of Heck and Horner–Wadsworth–Emmons reactions⁵ or Heck and Wittig reactions⁶ has also allowed the stepwise building of the conjugated

chain. Synthesis of stilbenes and poly(phenylenevinylene)s from haloarenes and ethene via two Heck reactions has been studied.⁷ We wish to report herein a one-pot synthesis of unsymmetrical (or symmetrical) *trans*-stilbene derivatives based on two sequential Heck-type reactions effected in the presence of tetraalkylammonium salt-based catalyst systems, using haloarenes and vinyltrimethylsilane as double bond equivalent.

We have recently reported that appropriate selection of tetraalkylammonium salt-based catalyst systems [Pd/MZ/QX] can permit, not only to accelerate Heck-type reactions, but also to direct them in order to realise these reactions with the desired selectivities.^{8–10} In particular, arylation of vinyltrimethylsilane can be efficiently oriented towards the formation of styrene derivatives.⁹ A double bond can thus be very effectively grafted onto an aromatic structure, offering the potential of constructing *trans*-stilbene derivatives **1** from haloarenes and vinyltrimethylsilane via two Heck-type reactions (Scheme 1).

In order to use twice the palladium catalyst and tetraalkylammonium salt, conditions have been found to realise the two sequential Heck-type reactions in the same flask. As shown in Table 1 (Scheme 2), unsymmetrical *trans*-stilbenes **1** can thus be obtained in high yields. Indeed, treatment in toluene, at room temperature, of an aryl iodide with an excess of vinyltrimethylsilane, in the presence of potassium fluoride, tetra-*n*-butylammonium chloride and catalytic amounts

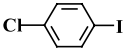

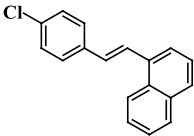
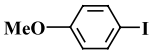
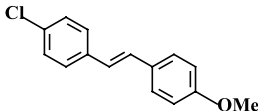
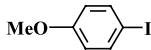
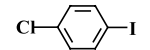
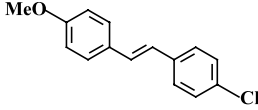

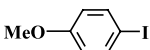
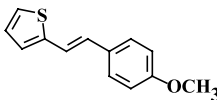
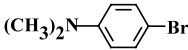
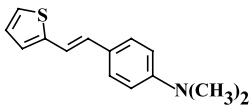

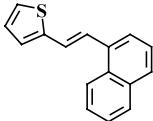


Scheme 1.

Keywords: palladium and compounds; Heck reactions; ammonium salts; vinyltrimethylsilane; resveratrol.

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Table 1. One-pot palladium-catalyzed synthesis of unsymmetrical stilbene derivatives (Scheme 2)^{a)}

Entry	ArX	Ar'X	PR ₃ /Pd b)	Temp ^{b)} (°C)	Product ^{c)} 1	Yield (%) ^{d), e)}
1			2	85		60
			0	65		(96)
2	"		0	65		72 (94)
3			0	65		(90)
4			1	85		68 (92)
5	"		2.4	105		60 (84)
6	"		2	85		66 (80)

^{a)} To a well-stirred suspension of anhydrous KF (3 equiv.) and *n*-Bu₄NCl (2 equiv.) in dry toluene, under a nitrogen atmosphere, were added ArX (1 equiv.), Pd(dba)₂ (0.04 equiv.) and vinyltrimethylsilane (5–6 equiv.). The resulting mixture was stirred at room temperature for 24h–48h. After addition of wet (2–3% H₂O) *N,N*-dimethylformamide, and (when stated) P(*o*-tol)₃ (as indicated by the PR₃/Pd molar ratio), the excess of vinyltrimethylsilane was removed under reduced pressure. K₂CO₃ (2.5 equiv.), and Ar'X (1 equiv.) were then added. Stirring was continued at the indicated temperature for 20h–24h. After cooling, addition of EtOAc, and filtration over Celite, the organic phase was washed (H₂O and brine), dried (MgSO₄), and the volatiles evaporated under reduced pressure. The crude product was purified by flash chromatography over silica gel or recrystallisation.

^{b)} Reaction conditions for the second arylation (PR₃/Pd molar ratio; oil bath temperature).

^{c)} All products were characterized by GC-MS analysis, ¹H NMR, ¹³C NMR, and UV spectroscopy.

^{d)} Unoptimized overall yields (from the corresponding ArX) of isolated products (isomeric purity > 98% by GC-MS analysis).

^{e)} Yields in parentheses were determined by GC analysis against an internal standard (*n*-hexadecane or *n*-heptadecane) and based on ArX (Scheme 2).

of bis(dibenzylideneacetone)palladium led to the formation of the corresponding styrenes.⁹ The excess of vinyltrimethylsilane was then removed under reduced pressure before effecting the second Heck reaction which was realised in wet *N,N*-dimethylformamide, in the presence of a [Pd/Base/QX] catalyst system¹¹ constituted by the palladium catalyst and tetra-*n*-butylammonium chloride already present in the reaction mixture, and added potassium carbonate. This second step can be realised in the presence or in the absence of ligand

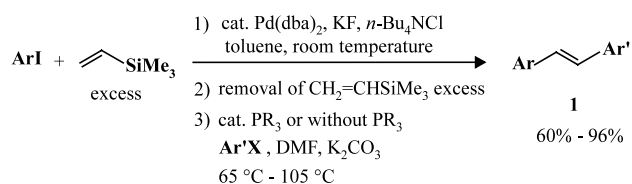
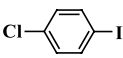
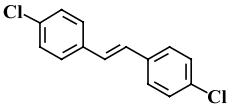
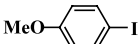
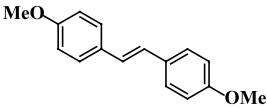

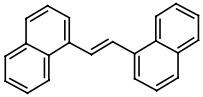
**Scheme 2.**

Table 2. One-pot palladium-catalyzed synthesis of symmetrical stilbene derivatives (Scheme 3)^{a)}

Entry	ArX	PR ₃ /Pd ^{b)}	Temp ^{b)} (°C)	Product ^{c)} 2	Yield (%) ^{d), e)}
1		0	65		72 (94)
2		1	85		62 (95)
3		0	65		70 (94)

^{a)} To a well-stirred suspension of anhydrous KF (3 equiv.) and *n*-Bu₄NCl (2 equiv.) in dry toluene, under a nitrogen atmosphere, were added ArX (2 equiv.), Pd(dba)₂ (0.04 equiv.) and vinyltrimethylsilane (1 equiv.). The resulting mixture was stirred at room temperature for 24h–40h. Wet (2–3% H₂O) N,N-dimethylformamide, K₂CO₃ (2.5 equiv.), and P(o-tol)₃ (when stated and as indicated by the PR₃/Pd molar ratio) were then added and stirring was continued for 24h at the indicated temperature. After cooling, addition of EtOAc, and filtration over Celite, the organic phase was washed (H₂O and brine), dried (MgSO₄), and the volatiles evaporated under reduced pressure. The crude product was purified by flash chromatography or recrystallisation.

^{b)} Reaction conditions for the second arylation (PR₃/Pd molar ratio; oil bath temperature).

^{c)} All products were characterized by GC–MS analysis, ¹H NMR, ¹³C NMR, and UV spectroscopy.

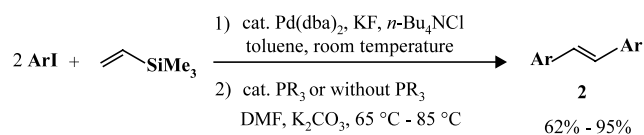
^{d)} Unoptimized yields of isolated products (isomeric purity > 98% by GC–MS analysis) based on ArX/2 (Scheme 3).

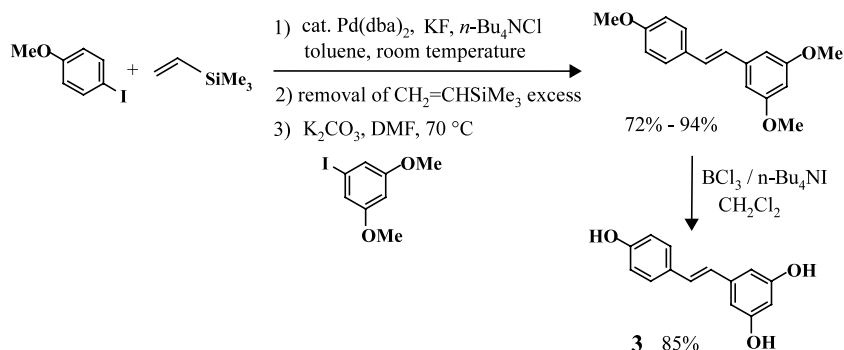
^{e)} Yields in parentheses were determined by GC analysis against an internal standard (*n*-hexadecane or *n*-heptadecane).

phosphine (Table 1, entries 1–3). The reported methodology can be applied to heteroaromatic halides (entries 4–6) for the synthesis of heteroaromatic *trans*-stilbenes whose interest has been highlighted.¹² The described one-flask, two-step reaction is highly chemo-, regio-, and stereoselective as coupled gas chromatography with mass spectrometry (GC–MS) analyses of the reaction mixtures indicated a nearly exclusive formation of stilbene derivatives, with a very high isomeric selectivity for the (*E*) configuration ranging between 96 and 99%.

Symmetrical stilbene derivatives **2** can be synthesized by a similar method (Table 2, Scheme 3). Treatment of 2 equiv. of an aryl iodide with 1 equiv. of vinyltrimethylsilane under the previously outlined arylation–desilylation conditions⁹ was followed by arylation in wet DMF, of the styrene derivatives formed in situ, in the presence of palladium catalyst and tetra-*n*-butylammonium chloride (already present in the reaction mixture) and potassium carbonate (added), without or with added triarylphosphine. GC–MS analyses of the reaction mixtures all show a highly selective formation of stilbene derivatives with a very high isomeric selectivity ranging between 95 and 99%. Although the (*E*)-configuration of symmetrical stilbene derivatives can not be deduced directly from ¹H NMR spectra, it can be expected from a Heck reaction, as resulting from a *syn*-addition–*syn*-elimination mechanism.¹³

The potential and efficiency of the described methodology has been illustrated by a concise, convenient, highly chemo-, regio-, and stereoselective synthesis of resveratrol **3** (*trans*-3,5,4'-trihydroxystilbene), a naturally occurring compound found in a variety of sources—including red wines—which has been shown to have multiple beneficial biological effects including protection against heart diseases and tumor development, prevention of oxidative damage and platelet aggregation.^{1a,14} As shown in Scheme 4, treatment of commercial 4-methoxyiodobenzene with vinyltrimethylsilane under the arylation–desilylation conditions⁹ followed by (i) removal of the excess of vinyltrimethylsilane under reduced pressure and (ii) arylation of the thus-formed 4-methoxystyrene by 3,5-dimethoxyiodobenzene,^{15,16} in a one-flask reaction, provides (*E*)-3,5,4'-trimethoxystilbene¹⁷ in 72% yield (94% GLC yield). Demethylation by the recently described¹⁸ boron trichloride/tetra-*n*-butylammonium iodide reagent cleanly affords resveratrol **3**¹⁹ in 85% yield.

**Scheme 3.**



Scheme 4.

In conclusion, we have developed an efficient, convenient, highly chemo-, regio-, and stereoselective one-flask, two-step synthetic methodology for the construction of unsymmetrical (or symmetrical) *trans*-stilbene derivatives based on two sequential Heck-type reactions, using tetraalkylammonium salt-based catalyst systems and vinyltrimethylsilane as double bond equivalent.

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and tetra-*n*-butylammonium chloride (1.65 g, 5.93 mmol) in dry toluene (5 mL), under a nitrogen atmosphere, were added 4-methoxyiodobenzene (0.75 g, 3.20 mmol), bis-(dibenzylideneacetone)palladium (69 mg, 0.12 mmol) and vinyltrimethylsilane (2.8 mL, 18.12 mmol). Following a 24–30 h stirring at room temperature and addition of wet (3% H₂O) *N,N*-dimethylformamide (7 mL), the excess of vinyltrimethylsilane was removed under reduced pressure. Potassium carbonate (1.1 g, 7.95 mmol) and 3,5-dimethoxyiodobenzene (0.85 g, 3.22 mmol) were then added and the reaction mixture was heated at 70°C (oil bath temperature) for about 24 h. After cooling, addition of ethyl acetate and filtration through Celite, the organic phase was washed (H₂O and brine), dried (MgSO₄), concentrated and purified by flash chromatography on silica gel (EtOAc:cyclohexane 1:4 as eluent) to provide a white solid (0.62 g, 72% yield, 94% GLC yield determined against *n*-hexadecane as internal standard); ¹H NMR (CDCl₃, 270 MHz, Me₄Si): δ 7.43 (d, *J*=8.6 Hz, 2H), 7.03 (d, *J*_{trans}=16.2 Hz, 1H), 6.88 (d, *J*=8.6 Hz, 2H), 6.87 (d, *J*_{trans}=16.2 Hz, 1H), 6.64 (d, *J*=2.3 Hz, 2H), 6.37 (t, *J*=2.3 Hz, 1H), 3.81 (s, 9H) ppm; ¹³C NMR (CDCl₃, 75 MHz): δ 161.0, 159.5, 139.8, 130.0, 128.8, 127.9, 126.6, 114.2, 104.4, 99.7, 55.4 ppm; MS (EI) *m/z* 270 (M⁺).

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19. **Resveratrol** (*trans*-3,5,4'-trihydroxystilbene): Under a nitrogen atmosphere, boron trichloride (9 mL of a 1.0 M solution in CH₂Cl₂) was added dropwise, at 0°C, to a well-stirred mixture of *trans*-3,5,4'-trimethoxystilbene (0.40 g, 1.48 mmol) and tetra-*n*-butylammonium iodide (3.26 g, 8.82 mmol) in dry dichloromethane (4 mL). Stirring was continued for 5–6 h while the reaction mixture was allowed to warm to room temperature. After controlling (by thin-layer chromatography) that the reaction was complete, saturated aqueous sodium hydrogen carbonate (10 mL) was added dropwise at 0°C and the resulting suspension stirred for 1 h at room temperature. The solid was filtered off, washed with CH₂Cl₂ and dissolved in a minimal amount of MeOH. Purification by flash chromatography on silica gel (ether:cyclohexane 4:1 as eluent) afforded *trans*-3,5,4'-trihydroxystilbene as a lightly beige powder (0.29 g, 85% yield); ¹H NMR (CD₃COCD₃, 270 MHz, Me₄Si): δ 8.53 (s, 1H), 8.27 (s, 2H), 7.42 (d, *J*=8.6 Hz, 2H), 7.06 (d, *J*_{trans}=16.4 Hz, 1H), 6.89 (d, *J*_{trans}=16.4 Hz, 1H), 6.86 (d, *J*=8.6 Hz, 2H), 6.57 (d, *J*=2.2 Hz, 2H), 6.30 (t, *J*=2.2 Hz, 1H) ppm; ¹³C NMR (CD₃COCD₃, 75 MHz): δ 159.6, 158.2, 140.9, 130.0, 129.2, 128.8, 126.8, 116.5, 105.7, 102.7 ppm.