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Chemoselective and Sequential Palladium-Catalyzed Couplings for the Generation of Stilbene Libraries via Immobilized Substrates

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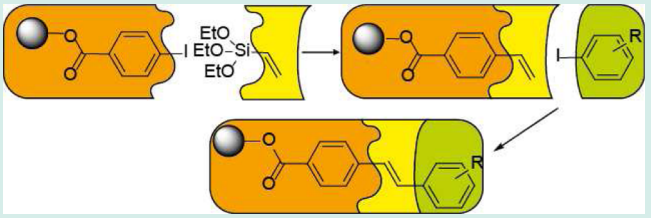
Supporting Information

ABSTRACT: A versatile palladium-catalyzed tandem synthetic sequence to afford *E*-stilbenes libraries has been developed. Excellent regio- and stereocontrol have been achieved by means of the sequence of Hiyama and Heck cross-couplings. Undesirable homocoupling byproducts were avoided employing immobilized substrates.



KEYWORDS: *palladium cross-coupling reactions, solid-phase organic synthesis, Hiyama coupling, Heck coupling*

Stilbene compounds are widely distributed in nature and have relevant applications in agriculture,[1] drug discovery[2] and material science.[3] Numerous stilbene-based derivatives, such as resveratrol,[4] piceatannol,[5] and pterostilbene[6] (Figure 1), have shown anti-inflammatory, antiproliferative, and

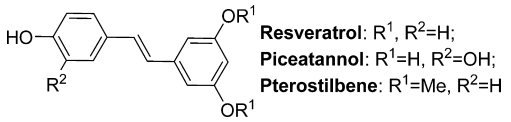
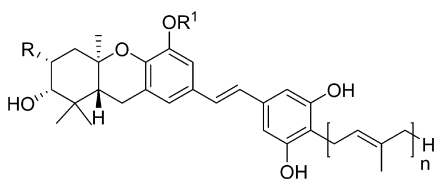


Figure 1. Structures of biologically relevant stilbenes.

antioxidant properties among others. Schweinfurthins[7] (Figure 2) are stilbene-related compounds which serve as potent and selective inhibitors in different cancer cell lines. Scheweinfurthins act on an unexploited molecular target, becoming promising drug candidates for untreated forms of this disease, such as glioblastoma multiforme. In addition, stilbenes are interesting substrates for diversity oriented synthesis (DOS)



Schweinfurthins: A: n=2, R=OH, R^1=H; **B:** n=2, R=OH, R^1=Me; **E:** n=1, R=OH, R^1=Me; **F:** n=1, R=H, R^1=Me; **G:** n=1, R, R^1=H

Figure 2. Some members of the schweinfurthin family.

strategies, enabling fast and easy diversification by increasing molecular complexity.[8]

The development of new approaches for the generation of single and double C−C bonds with regio- and stereoselectivity control remains a challenge in organic synthesis. Methodologies involving the use of inexpensive, easy to handle, low toxicity reagents and catalysts are highly desirable since they enable mild reaction conditions and good yields.[9]

Most reported strategies for the synthesis of symmetrical and asymmetrical (*E*)-1,2-substituted diarylethenes[10] involve reaction conditions with limited diastereoselectivity and low functional group tolerance. These include Wittig reactions, cross metathesis of vinyl arenes and catalytic couplings, such as Heck, Suzuki−Miyaura, Stille, and Hiyama reactions.[10] The presence of homocoupling products is one of the main drawback for these catalytic techniques.[11]

An interesting high-yielding procedure for the synthesis of diarylethenes with high regio- and stereoselectivity, using safe, stable and low-toxicity reagents, is the Hiyama−Heck tandem reaction.[12] However, when this strategy was used in solution, the formation of undesirable homocoupling products is difficult to elude.[11] This problem might be solved by applying a Hiyama + filtration + Heck tandem sequence on polymer-supported substrates,[13] as a practical way to decrease the formation of byproducts. For solid-phase coupling reactions, spatial separation between the reactive sites in the immobilized substrate made its homodimerization a less favorable process. Similarly, the homodimer of the nonimmobilized substrate remains in the

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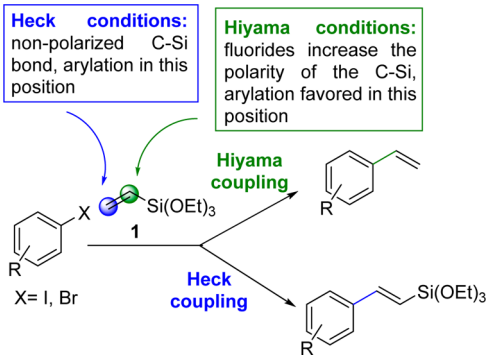
solution phase and can be removed by a simple filtration.[14] Besides, process simplicity would allow fast synthesis of unexplored structures, resulting in a useful tool for DOS development. In this work, we report the first solid-phase-based tandem Hiyama−Heck cross-couplings and their application in stilbene synthesis.

Vinyltriethoxysilane has two reactive positions for undergoing cross-coupling in the presence of Pd catalyst (shown in blue and green, Scheme 1). Each chemically differentiable

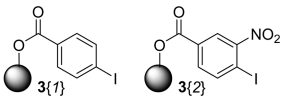
Scheme 1. Chemically Differentiable Carbon Atoms of 1



reaction site can give a unique product with high regio- and stereocontrol, by setting the conditions and additives. Under Hiyama conditions, fluoride ions present in the reaction mixture would react with the silicon atom generating a pentacoordinated transition state, increasing the C−Si bond polarity and therefore, facilitating the cross-coupling reaction. Conversely, under Heck conditions, without fluorides influencing the olefin reactivity, carbon−carbon bond formation occurs at the more electron-deficient and less hindered carbon.

For the development of the proposed synthetic strategy, Hiyama cross-coupling conditions were applied on Wang resin-supported aryl iodide 3{*1*} (Scheme 2 and Figure 3). 3{*1*} was refluxed in THF in the presence of 5 equiv of triethoxyvinylsilane (**1**), 10 mol % of tetrakis(triphenylphosphine)-palladium(0) and 5 equiv of TBAF for 5 h.[15] The exclusive formation of 4{*1*} and absence of the product derived from Heck coupling 5{*1*}, was verified by spectroscopic analysis of a crude mixture after cleaving an aliquot from the resin. Then Heck conditions were applied to the immobilized styrene 4{*1*}.[16] This compound was treated with iodobenzene 6{*1*}, 10 mol % of $Pd_2(dba)_3$, P(*o*-tolyl)$_3$ and 5 equiv of TEA in DMF as solvent, heating at 110 °C during 24 h. To calculate purity and reaction yield, 7{*1,1*} was cleaved from the resin and

Polymer supported aryl iodides 3



Non-inmobilized aryl halides 6

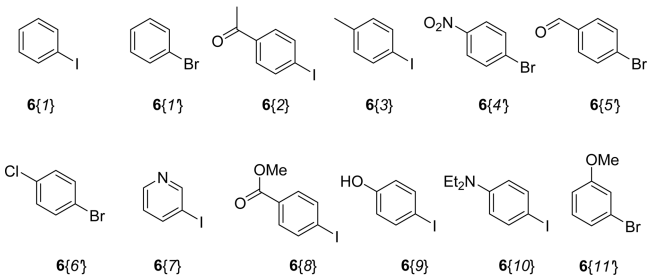


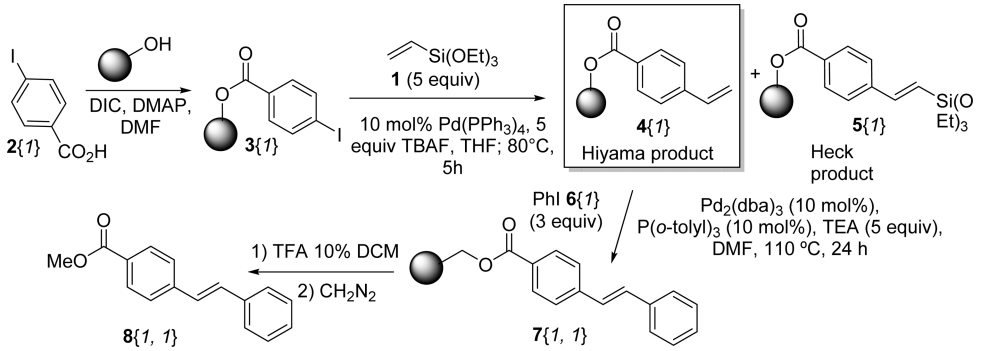
Figure 3. Structures and numbering of building blocks.

methylated. ^{1}H NMR analysis of the crude showed the presence of 8{*1,1*} as main product and absence of the methyl esters derived from 4{*1*} and 5{*1*}. Compound 8{*1,1*} was obtained in 51% yield after purification by column chromatography. Increased reaction time (7 h) resulted in decreased overall yields for the Hiyama reaction, probably due to decomposition. A similar effect was observed for the Heck cross-coupling performed without TEA, evidencing incomplete transformation by the presence of the corresponding unreacted styrene (acid derivative of 4{*1*}).

As discussed previously, changing the order of the reactions sequence (Heck + filtration + Hiyama), should give the same product. Then, resin 3{*1*} was treated with triethoxyvinylsilane (**1**) under Heck conditions (Scheme 3). The presence of 5{*1*} was confirmed by gel-phase ^{13}C NMR spectrum that showed signals at 58.9 and 18.3 ppm, corresponding to the carbons of the ethoxy groups. The immobilized vinyl silane 5{*1*} was finally transformed into the stilbene 7{*1,1*} by applying Hiyama cross-coupling conditions. After cleavage, esterification and further purification by column chromatography, 8{*1,1*} was obtained in an overall yield of 30%.

Direct comparison of the two alternative synthetic routes to 8{*1,1*} indicates that the first strategy (Hiyama + filtration + Heck) was more efficient. These results confirm that changes in the reaction conditions over the triethoxyvinylsilane (**1**) are enough to obtain selectively either Heck or Hiyama product. Considering the Hiyama + filtration + Heck sequence the best option (entry 1, Table 1), we decided to validate the Heck

Scheme 2. Solid-Phase Synthesis of 8{*1,1*} by Sequential Hiyama−Heck Cross-Couplings



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Scheme 3. Solid-Phase Synthesis of 8{*1,1*} by Sequential Heck−Hiyama Cross-Couplings

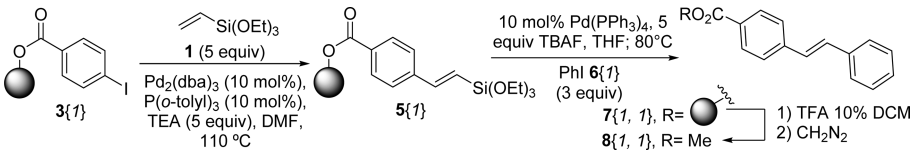
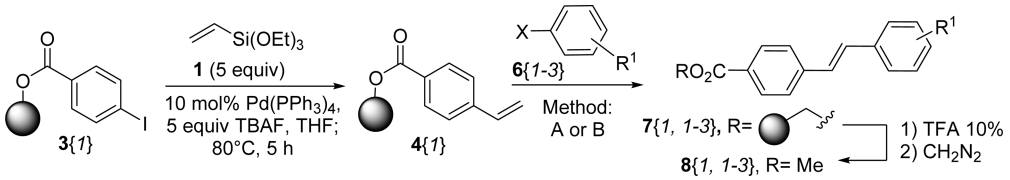


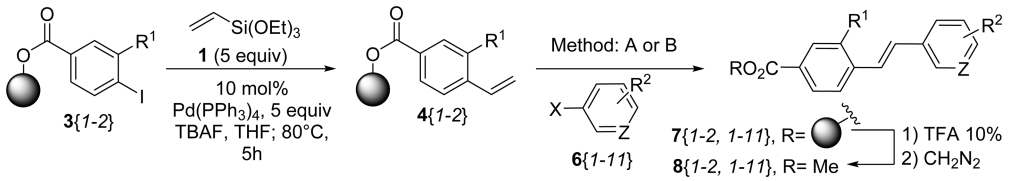
Table 1. Evaluation of Conditions of Hiyama−Heck Tandem Reactions Using the Immobilized Aryl Iodide 3{*1*}



entry	halide	X	R^1	Heck conditions[a]	product	yield (%)[b]
1	**6**{*1*}	I	H	A	**8**{*1,1*}	73 (51)
2	**6**{*1′*}	Br	H	A	**8**{*1,1*}	57 (36)
3	**6**{*1′*}	Br	H	A[c]	**8**{*1,1*}	51[d]
4	**6**{*2*}	I	4-COMe	A	**8**{*1,2*}	63[d]
5	**6**{*3*}	I	4-Me	A	**8**{*1,3*}	45 (10)
6	**6**{*3*}	I	4-Me	B	**8**{*1,3*}	69 (40)

[a]Method A: 10 mol % $Pd_2(dba)_3$ and P(*o*-tolyl)$_3$, 5 equiv TEA, DMF, 110 °C, 24 h. Method B: 50 mol % $Pd(OAc)_2$, 10 equiv TEA, 0,5 equiv Bu_4NCl, DMF, 18 h. 110 °C. [b]Yield of **8**, calculated by weighing the crude mixture, prior to purification (based on initial loading level, five reaction steps). Data in parentheses are isolated yields. [c]0.1 equiv of Bu_4NCl was added. [d]From ^1H NMR spectrum of the crude mixture, which contains starting material.

Table 2. Substrate Scope for the Sequential Hiyama−Heck Cross-Couplings Using Immobilized Aryl Iodides



entry	X	Z	R^2	R^1	Heck conditions[a]	product	yield (%)[b]
1	I	CH	H (**6**{*1*})	H (**4**{*1*})	A	**8**{*1,1*}	51
2	Br	CH	H (**6**{*1′*})	H (**4**{*1*})	A	**8**{*1,1*}	36
3	I	CH	H (**6**{*1*})	NO_2 (**4**{*2*})	B	**8**{*2,1*}	36
4	Br	CH	4-NO_2 (**6**{*4′*})	H(**4**{*1*})	B	**8**{*1,4*}	65
5	Br	CH	4-NO_2 (**6**{*4′*})	NO_2 (**4**{*2*})	B	**8**{*2,4*}	30
6	Br	CH	4-CHO (**6**{*5′*})	H (**4**{*1*})	A	**8**{*1,5*}	38
7	Br	CH	4-Cl (**6**{*6′*})	H (**4**{*1*})	A	**8**{*1,6*}	44
8	I	CH	4-COMe (**6**{*2*})	H (**4**{*1*})	B	**8**{*1,2*}	47
9	I	CH	4-COMe (**6**{*2*})	NO_2 (**4**{*2*})	B	**8**{*2,2*}	79
10	I	N	H (**6**{*7*})	H (**4**{*1*})	A	**8**{*1,7*}	24
11	I	CH	4-Me (**6**{*3*})	H (**4**{*1*})	A	**8**{*1,3*}	10
12	I	CH	4-Me (**6**{*3*})	H (**4**{*1*})	B	**8**{*1,3*}	40
13	I	CH	4-Me (**6**{*3*})	NO_2 (**4**{*2*})	B	**8**{*2,3*}	21
14	I	CH	4-CO_2Me (**6**{*8*})	H (**4**{*1*})	A	**8**{*1,8*}	8
15	I	CH	4-CO_2Me (**6**{*8*})	H (**4**{*1*})	B	**8**{*1,8*}	46
16	I	CH	4-OH (**6**{*9*})	H (**4**{*1*})	A	**8**{*1,9*}	21
17	I	CH	4-OH (**6**{*9*})	H (**4**{*1*})	B	**8**{*1,9*}	15
18	I	CH	4-NEt_2 (**6**{*10*})	H (**4**{*1*})	B	**8**{*1,10*}	19
19	Br	CH	3-OMe (**6**{*11′*})	H (**4**{*1*})	B	**8**{*1,11*}	10

[a]Method A: 10 mol % $Pd_2(dba)_3$ and P(*o*-tolyl)$_3$, 5 equiv TEA, DMF, 110 °C, 24 h. Method B: 50 mol % $Pd(OAc)_2$, 10 equiv TEA, 0,5 equiv Bu_4NCl, DMF, 18 h. 110 °C. [b]Overall isolated yield of **8** after column chromatography (based on initial loading level, five reaction steps).

reaction using bromo derivatives. In this case, using bromobenzene as substrate (**6**{*1′*}), compound **8**{*1,1*} was obtained in 36% yield after purification (entry 2). Addition of catalytic amounts of tetrabutylammonium chloride is described in literature as a valid tool to produce higher yields.[16a,b] However, when this salt was added to the Heck reaction under conditions described in entry 2, lower yields were obtained (entry 3). Although reaction performance for the bromide

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substrates (**6**{*1′*}, entry 2) was lower than in the case of iodides (**6**{*1*}, entry 1), yields were still acceptable. Therefore, we can conclude that both halides could be potentially employed as starting materials for this reaction improving substrate availability for the generation of prospective libraries. Testing this methodology for aryl iodides **6**{*2*} (R^1 = 4-COMe) and **6**{*3*} (R^1 = 4-Me) resulted in lower yields (entries 4 and 5, Table 1). As a consequence, additional Heck reaction conditions were evaluated. Substantial improvement was found for the iodide **6**{*3*} using 50 mol % of $Pd(OAc)_2$, 10 equiv of triethylamine, 0.5 equiv of tetrabutylammonium chloride in DMF during 18 h at 110 °C (entry 6).

Accordingly, using Hiyama and the two Heck methodologies previously described, a library of stilbene derivatives was synthesized, using substrates with different structural and electronic features (Table 2). Compounds **8**{*1−2,1−11*} could be obtained in acceptable to high isolated yields (five reaction steps). Crude mixtures showed very high purity, and excellent *trans*-selectivity (the *Z* isomers could not be detected at all).[17] Best efficiencies for the Heck reaction were obtained when aryl halides bearing electron-withdrawing groups served as substrates (entries 3−9, 14, and 15).[18] Withdrawing substituents led to an increase in the C−X bond polarization, facilitating oxidative addition in the palladium catalytic cycle, which may be responsible for the better efficiency. This effect is quite evident when comparing entries 9 and 13. Using the same immobilized vinyl substrate **4**{*2*} and aryl halides with different electronic characteristics in the Heck reaction, we noticed a decrease in yields from 79 to 21% when replacing an electron-withdrawing substituent (*p*-COMe) by a donating one (*p*-Me).

In conclusion, we have developed an efficient solid-phase strategy based on a palladium cross-coupling tandem reaction for the fast generation of stilbenes. A library of multifunctional olefins with structural diversity was prepared from substrates with different steric and electronic properties, using both aryl iodides and bromides for the Heck cross-coupling. Products were obtained with excellent *E* stereoselectivity. This strategy could be potentially applied for the synthesis of compounds with higher structural complexity and prospective biological activity. Biological activity against several tumor cell lines for the hereby-synthesized compounds is currently under evaluation.

EXPERIMENTAL PROCEDURES

Procedure for Immobilization of Aryl Iodide 3{*1*}. Wang resin (0.2 g, 1.1 mmol/g, 0.22 mmol) was swelled by gentle stirring in anhydrous DMF (5 mL). Then, 4-iodobenzoic acid **2**{*1*} (0.098 g, 0.66 mmol), DCC (*N,N′*-diisopropylcarbodiimide) (0.102 mL, 0.66 mmol), and DMAP (catalytic amount) were added. The mixture was stirred overnight at room temperature. After filtration, the resin was sequentially washed with CH_2Cl_2 (×3), DMF (×3), EtOAc (×3), MeOH (×3), and CH_2Cl_2 and, finally, dried under high vacuum thus obtaining the immobilized aryl iodide **3**{*1*}. Mass recovery was used to determine resin loading after cleavage of an aliquot with 10% TFA/CH_2Cl_2. In general, coupling was achieved with greater than 95% efficiency.

Representative Procedure for the Solid-Phase Hiyama Cross−Coupling Reaction. Support-bound aryl halide **3**{*1*} (0.88 mmol/g, 0.18 mmol) was suspended in anhydrous THF (5 mL), and were added in sequential order under a nitrogen atmosphere $Pd(PPh_3)_4$ (0.020 g, 10 mol %), vinyltriethoxysilane **1** (0.189 mL, 0.9 mmol) and TBAF (0.9 mL, 1 M in THF). The flask was fitted with a condenser and the reaction mixture was stirred 5 h at 80 °C. Subsequently, the resin was filtered and washed successively with CH_2Cl_2 (×3), THF (×3), DMF (×3), and MeOH (×3), and finally, with CH_2Cl_2 thus obtaining the support-bound vinyl arene **4**{*1*}. Then, the resin was dried under high vacuum and used for the Heck cross-coupling reaction.

Representative Procedure for the Solid-Phase Heck Cross-Coupling Reaction: *Method A.* Support-bound vinyl arene **4**{*1*} (0.96 mmol/g, 0.19 mmol) was suspended in anhydrous DMF (5 mL), and were added in sequential order under a nitrogen atmosphere, $Pd_2(dba)_3$ (0.018 g, 10 mol %), P(*o*-tolyl) (0.005 g,10 mol %), aryl halide **6**{1} (0.064 mL, 0.57 mmol), and TEA (133 mL, 0.95 mmol). The flask was fitted with a condenser and the reaction mixture was stirred 24 h at 110 °C. Subsequently, the resin was filtered and washed successively with CH_2Cl_2 (×3), THF (×3), DMF (×3), MeOH (×3), and finally, with CH_2Cl_2. After drying under high vacuum, the compound was cleaved from the support with 5 mL of a 10% TFA in CH_2Cl_2 for 50 min at room temperature. Then the mixture was filtered and washed with CH_2Cl_2 (×2), and the filtrate was evaporated under reduced pressure. Esterification with diazomethane afforded the crude product that was analyzed by ^{1}H NMR and GC/MS and then purified by column chromatography (hexane-EtOAc), yielding 20 mg of pure (*E*)-Methyl 4-styrylbenzoate (**8**{*1,1*}) (51%).

Method B. Support-bound vinyl arene **4**{*1*} (0.96 mmol/g, 0.19 mmol) was suspended in anhydrous DMF (5 mL), and $Pd(OAc)_2$ (0.021 g, 50 mol %), Bu_4NCl (0.026 g, 0.095 mmol), aryl halide **6**{3} (0.207 g, 0.95 mmol), and TEA (0.267 mL, 1.9 mmol) were added in sequential order under a nitrogen atmosphere. The flask was fitted with a condenser, and the reaction mixture was stirred 18 h at 110 °C. Subsequently, the resin was filtered and washed successively with CH_2Cl_2 (×3), THF (×3), DMF (×3), MeOH (×3), and finally with CH_2Cl_2. After drying under high vacuum, the compound was cleaved from the support with 5 mL of a 10% TFA in CH_2Cl_2 for 50 min at room temperature. Then the mixture was filtered, washed with CH_2Cl_2 (×2) and the filtrate was evaporated under reduced pressure. Esterification with diazomethane afforded the crude product that was analyzed by ^{1}H NMR and GC/MS and then purified by column chromatography (hexane-EtOAc) yielding 17 mg of pure (*E*)-methyl 4-(4-methylstyryl)benzoate (**8**{*1,3*}) (40%).

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscombsci.6b00023.

Experimental details and spectroscopic data: ^{1}H NMR and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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