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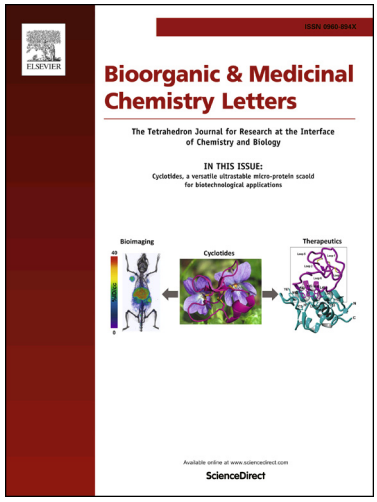

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PII: S0960-894X(18)30302-0
DOI: https://doi.org/10.1016/j.bmcl.2018.04.004
Reference: BMCL 25751

To appear in: *Bioorganic & Medicinal Chemistry Letters*

Received Date: 2 February 2018
Revised Date: 31 March 2018
Accepted Date: 2 April 2018

Please cite this article as: Rau, H.H., Werner, N.S., Stereospecific synthesis of (*E*)-stilbene derivatives by palladium-catalyzed Suzuki-Miyaura cross-coupling reaction, *Bioorganic & Medicinal Chemistry Letters* (2018), doi: https://doi.org/10.1016/j.bmcl.2018.04.004

Stereospecific synthesis of (*E*)-stilbene derivatives by palladium-catalyzed Suzuki-Miyaura cross-coupling reaction

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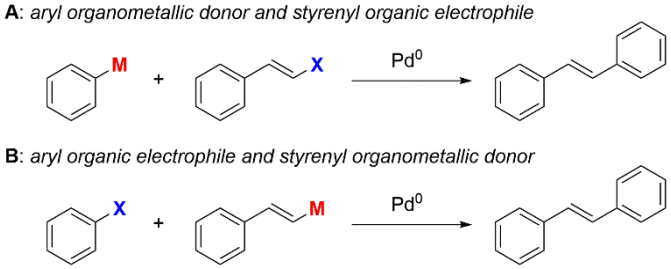
Abstract

A general procedure for the stereospecific synthesis of (*E*)-stilbene derivatives by palladium-catalyzed Suzuki-Miyaura cross-coupling reaction of (*E*)-2-phenylethenylboronic acid pinacol ester with aryl bromides was investigated. (*E*)-2-phenylethenylboronic acid pinacol ester was prepared by 9-BBN-catalyzed hydroboration of phenylacetylene with pinacolborane. This reagent undergoes facile palladium-catalyzed cross-coupling with a diverse set of aryl bromides to provide the corresponding (*E*)-stilbene derivatives in moderate to good yield. The use of the sterically bulky *t*-Bu_3PHBF_4 ligand was crucial to the successful coupling of electron-rich and electron-poor aryl bromides.

(*E*)-Stilbene derivatives are known to exhibit a variety of interesting biological activity.[1] In particular, the natural product resveratrol, found in red wine, has been widely studied after it was associated with the low incidence of cardiovascular disease in a French population with a diet that is relatively high in saturated fat.[2] Simple, synthetic (*E*)-stilbene derivatives have also been identified to have value as potential therapeutics.[1b–d] The stilbene alkene geometry fundamentally changes the overall structure of the molecule and can affect the biological activity.[1e–h] Therefore, it is important that synthetic methods are developed for the preparation of stilbene derivatives with high geometrical selectivity.

The Suzuki-Miyaura cross-coupling reaction provides a mild and selective method for the construction of bonds between all hybridizations of the carbon atom.[3] Increasingly, the study of the Suzuki-Miyaura cross-coupling reaction has provided a number of solutions for the synthesis of complex organic molecules[4], and has elucidated many of the mechanistic details of this important reaction.[5] Surprisingly, a review of the literature provided very few examples of the general preparation of simple (*E*)-stilbene derivatives by Suzuki-Miyaura reaction.[6,7] Therefore, a general method for the synthesis of (*E*)-stilbene derivatives by palladium-catalyzed Suzuki-Miyaura cross-coupling reaction was investigated.

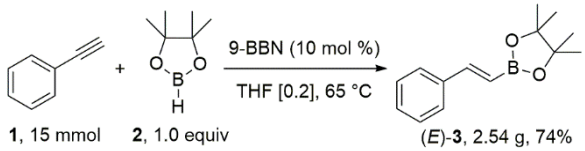
Initially, two polar disconnections were entertained for the synthesis of (*E*)-stilbene derivatives by palladium-catalyzed Suzuki-Miyaura cross-coupling: (**A**) an aryl organometallic donor with a 2-phenylethenyl (styrenyl) organic electrophile, or (**B**) an aryl organic electrophile and a styrenyl organometallic donor (Scheme 1). Couplings of type **A** were recently studied by Lipshutz et. al and the effect of ligands on the geometrical selectivity of the couplings was reported.[8] It was found in these studies that the ligand additive had the greatest effect on the *E*/*Z* composition of the product when (*E*)-1-iodooctene was used as the organic electrophile. The ligand dependent mixtures of isomeric alkene products led us to investigate couplings of type **B** for a general preparation of geometrically pure (*E*)-stilbene derivatives.



Scheme 1. Analysis of the polar disconnection of palladium-catalyzed cross-coupling reagents.

Couplings of type **B** that employed (*E*)-2-phenylethenylboronic acid were reported to be stereospecific.[6] Product yields are higher when (*E*)-2-phenylethenylboronic acid rather than the corresponding catechol boronic ester is used as the organometallic donor.[6b] However, the boronic acid is typically synthesized by hydrolysis of the corresponding catechol boronic ester, and its isolation can be tedious.[7] Moreover, the catechol boronic ester is air-sensitive.[6b] Therefore, it was encouraging that (*E*)-2-phenylethenylboronic acid pinacol ester (*E*)-**3** was found to be the preferred organometallic donor in a stereospecific cross-coupling with aryl nonaflates.[7] Yet, in this report the pinacol boronic ester (*E*)-**3** was also synthesized from the sensitive catechol derivative. Thus, the focus of this work was broadened to include a streamlined synthesis of (*E*)-**3** by direct hydroboration reaction with commercially available pinacolborane **2**.

The synthesis of (*E*)-stilbene derivatives by palladium-catalyzed Suzuki-Miyaura cross-coupling reaction required the preparation of (*E*)-**3**. It was proposed that (*E*)-**3** could be prepared by direct hydroboration of pinacolborane. However, the hydroboration reaction of phenylacetylene **1** with pinacolborane **2** is sluggish and only trace product was observed after 7 h in refluxing THF (65 °C). Gratifyingly, 10 mol % of 9-borobicyclo[3.3.1]nonane (9-BBN) could be used to catalyze the hydroboration reaction (Scheme 1).[9,10] The reaction produces only the (*E*)-**3** isomer, is complete within 20 min, and no alkylborane products were observed after a simple aqueous work-up. In addition, (*E*)-**3** was purified by flash chromatography and isolated in good yield.



Scheme 2. Synthesis of (*E*)-**3** by 9-BBN catalyzed hydroboration of phenylacetylene with pinacolborane.

The pinacol boronic ester (*E*)-**3** was found to cleanly couple with **4a** to provide the desired product (*E*)-**5a** (Table 1, entry 1). The effect of reaction parameters on product yield was then studied. Increasing the amount of (*E*)-**3** from 1.0 to 1.2 equiv increased the yield of (*E*)-**5a** (entries 1 and 2). Decreasing the reaction temperature from 90 °C to 70 °C decreased the yield of (*E*)-**5a** (entries 2 and 3). The use of $Pd(OAc)_2$ provided a superior yield than $Pd_2(dba)_3$ (entries 2 and 4). Lower yields were observed when Cs_2CO_3 and *t*-BuOK were used as the base (entries 2, 5 and 6). Interestingly, the combination of Cs_2CO_3 as base and dioxane as solvent provided a very low yield of (*E*)-**5a** (entry 7). The use of DMF as reaction solvent was found to provide the best product yield (entries 2, 8–10). The highest yield of (*E*)-**5a** was obtained when Ph_3P was used as the ligand (entries 2, 11–13).

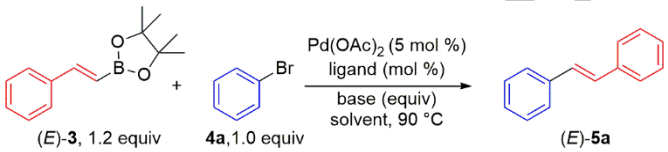
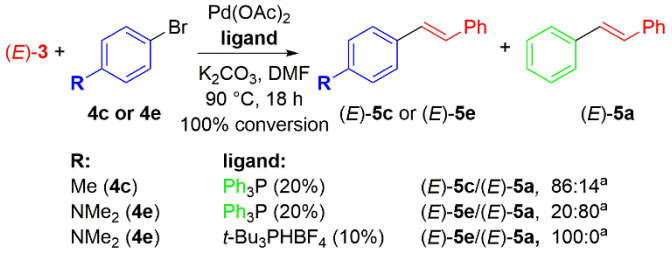


Table 1. Optimization of the palladium-catalyzed Suzuki-Miyaura cross-coupling reaction of (*E*)-**3** and **4a**.

entry	ligand, %	base, equiv	solvent	yield,[a] %
1[b]	Ph_3P, 20	K_2CO_3, 1.1	DMF	75
2	Ph_3P, 20	K_2CO_3, 1.1	DMF	79
3[c]	Ph_3P, 20	K_2CO_3, 1.1	DMF	62
4[d]	Ph_3P, 20	K_2CO_3, 1.1	DMF	43
5	Ph_3P, 20	KO*t*-Bu, 1.1	DMF	73
6	Ph_3P, 20	Cs_2CO_3, 1.1	DMF	73
7	Ph_3P, 20	Cs_2CO_3, 1.1	dioxane	25
8	Ph_3P, 20	K_2CO_3, 1.1	dioxane	77
9	Ph_3P, 20	K_2CO_3, 1.1	DMSO	66
10	Ph_3P, 20	K_2CO_3, 1.1	toluene	NR[e]
11	JohnPhos, 10	K_2CO_3, 1.1	DMF	53
12	SPhos, 10	K_2CO_3, 1.1	DMF	56
13	*t*-Bu_3PHBF_4, 10	K_2CO_3, 1.2	DMF	69

[a]Yield of isolated, purified product.
[b]1.0 equiv of (*E*)-**3** was used.
[c]Reaction temperature of 70 °C.
[d]$Pd_2(dba)_3$ (5 mol %) was used as the palladium source.
[e]Palladium black and no cross-coupling reaction was observed.



Scheme 3. An (*E*)-**5a** by-product was observed in reactions that used the Ph_3P ligand and an electron-rich aryl bromide substrate.
[a]GC peak area ratio.

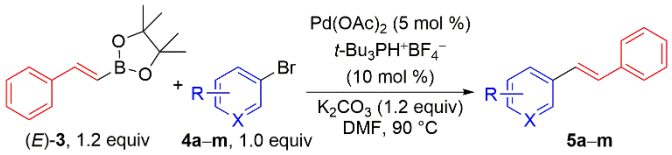
The reaction conditions of (*E*)-**3** (1.2 equiv), aryl bromide (1.0 equiv), $Pd(OAc)_2$ (5%), Ph_3P (20%), K_2CO_3 (1.1 equiv), DMF, and a 90 °C reaction temperature were then used to evaluate the scope of compatible aryl bromides (Scheme 3). Surprisingly, an (*E*)-**5a** by-product, presumably the result of phenyl group transfer from Ph_3P,[11] was observed under these reaction conditions when electron-rich aryl bromides were used as substrates. Specifically, the reaction of (*E*)-**3** with **4c** provided an 86:14, (*E*)-**5c**/(*E*)-**5a** which increased to 20:80 favoring the (*E*)-**5a** by-product when the more electron-rich aryl bromide **4e** was used. The (*E*)-**5a** by-product was not observed in reactions that used *t*-Bu_3PHBF_4 as the ligand.[12] Therefore, *t*-Bu_3PHBF_4 was used as the ligand to evaluate other aryl bromide substrates.

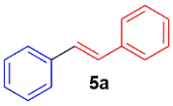
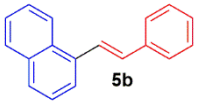
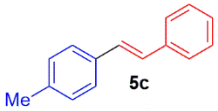
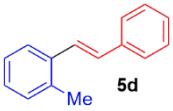
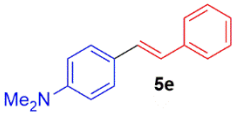
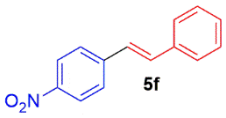
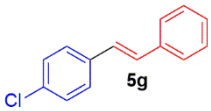
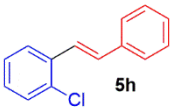
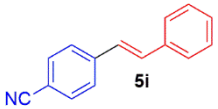
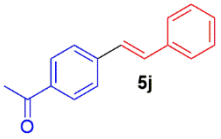
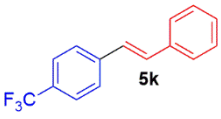
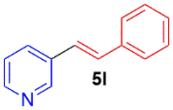
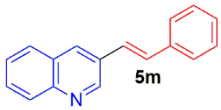
The scope of compatible aryl bromides in the cross-coupling reaction with (*E*)-**3** when *t*-Bu_3PHBF_4 was used as the ligand was studied (Table 2).[13] The electronically neutral aryl bromides **4a** and **4b** were found to be good substrates in this reaction (entries 1–2). The sterically hindered aryl bromides **4d** and **4h** successfully coupled under these conditions (entries 4 and 8). Importantly, the electron-rich substrates **4e** and **4c** provided clean conversion (GC) to the desired (*E*)-stilbene derivative. (entries 3 and 5). Substrates bearing electron-poor groups (e.g. **4g**, **4f**, **4i**, **4j**, and **4k**) coupled well under these reaction conditions (entries 7, 9–11). The heterocyclic aryl bromides **4l** and **4m** provided the corresponding (*E*)-stilbene derivative in good isolated yield. In addition, GC analysis of crude reaction aliquots showed complete stereochemical retention of (*E*)-**3** in all cases studied.

In conclusion, (*E*)-stilbene derivatives can be readily prepared by the stereospecific palladium-catalyzed Suzuki-Miyaura cross-coupling reaction of (*E*)-**3** and aryl bromides. The reagent (*E*)-**3** is easily prepared by 9-BBN catalyzed hydroboration reaction of **1** and **2**. This circumvents the use of the air-sensitive catechol boronic

ester intermediate. The use of *t*-Bu_3PHBF_4 as the ligand was found to be crucial to the successful coupling of (*E*)-**3** with a variety of electronically and sterically diverse substrates. Moderate to good yield of the (*E*)-stilbene derivatives **5a–m** were obtained. Complete retention of the stereochemistry of the boronic ester (*E*)-**3** was observed in all cases studied.

Table 2. Scope of *trans*-stilbene derivatives synthesized by palladium-catalyzed Suzuki-Miyaura cross-coupling reaction.[a]



entry	product	yield,[b] %
1	 **5a**	69
2	 **5b**	73
3	 **5c**	52
4	 **5d**	53
5	 **5e**	54
6	 **5f**	73
7	 **5g**	66
8	 **5h**	44
9	 **5i**	76
10	 **5j**	63
11	 **5k**	67
12	 **5l**	67
13	 **5m**	83

[a]Reactions were performed on at least 0.5 mmol scale.
[b]Yield of isolated, purified product.

Acknowledgments

We are grateful to Southern Utah University for a Faculty Project Fund Grant (N.S.W.), a Walter Maxwell Gibson Research Fellowship (H.H.R.), and a L. S. and Aline W. Skaggs Research Grant (H.H.R.) to generously support this work.

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9. Preparation of (*E*)-**3**. To an oven-dried, 250 mL round-bottomed flask, containing a magnetic stir-bar, equipped with a reflux condenser capped with septum, purged with Ar, and under a balloon of Ar was added THF (70 mL), phenylacetylene (1.65 mL, 15 mmol, 1.0 equiv), pinacolborane (2.18 mL, 15 mmol, 1.0 equiv), and 9-BBN (3.00 mL, 1.5 mmol, 0.1 equiv). An additional volume of THF (5 mL) was used to wash all of the reagents into the flask. The flask was then placed in a preheated oil bath (80 °C) and allowed to reflux for 20 min. The reaction was then cooled to rt, and purified by aqueous work-up and flash chromatography (15 g silica gel, 20 mm column diameter, 5% EtOAc/hexane eluent) to provide 2.54 g (74%) of (*E*)-**3** as a clear, colorless oil. ^{1}H NMR (400 MHz, CDCl3): δ 7.48–7.45 (m, 2 H), 7.40 (d, *J* = 18.5, 1 H), 7.33–7.23 (m, 3 H), 6.17 (d, *J* = 18.5, 1 H), 1.29 (s, 12 H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 149.5, 137.5, 128.9, 128.6, 127.1, 83.4, 24.9; IR (neat): 3080 (w), 3054 (w), 3018 (w), 2978 (w), 2928 (w), 1623 (m), 1577 (w), 1495 (w), 1450 (m), 1391 (m), 1371 (m), 1346 (s), 1322 (s), 1271 (m), 1237 (m), 1210 (m), 1142 (s), 1109 (w), 997 (m), 969 (m), 899 (m), 851 (m), 748 (m), 692 (m), 660 (w), 641 (w); MS (EI, 70 eV) 230 ($[M]^+$, 49), 229 (12), 215 (24), 157 (11), 145 (38), 144 (69),

143 (10), 131 (56), 130 (100), 129 (92), 118 (16), 114 (14), 105 (31), 104 (15), 103 (16), 85, (10), 78 (12), 77 (21); TLC (hexane/EtOAc, 95:5) R_f 0.53.

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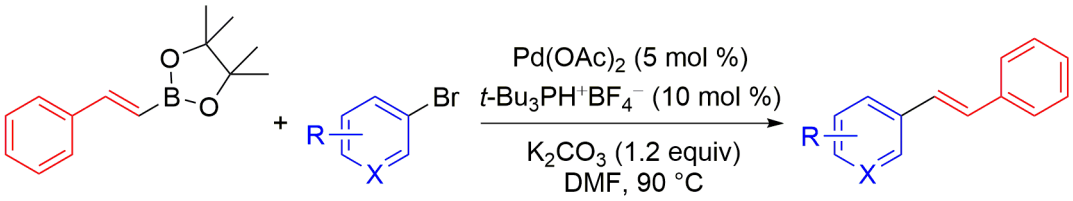
13. Preparation of (*E*)-**5a**. To an oven-dried, 25 mL round-bottomed flask, containing a magnetic stir-bar was added $Pd(OAc)_2$ (5.90 mg, 0.026 mmol, 0.05 equiv), *t*-Bu_3PHBF_4 (15.2 mg, 0.52 mmol, 0.10 equiv), and K_2CO_3 (87.1 mg, 0.63 mmol, 1.2 equiv). (*E*)-2-phenylethenylboronic acid pinacol ester (145 mg, 0.63 mmol, 1.2 equiv) was weighed, dissolved in DMF (2.63 mL), and then added to the solid reagents. The flask was capped with a septum, purged with Ar for 10 min, and bromobenzene (55.3 μL, 0.52 mmol, 1.0 equiv) was added by syringe. The flask was then placed in a preheated oil bath (90 °C) and allowed to stir under a balloon of Ar for 2 h. The reaction was then cooled to rt, and purified by aqueous work-up and flash chromatography (15 g silica gel, 10 mm column diameter, hexane eluent) to provide 63.0 mg (66%) of (*E*)-**5a** as a white solid. ^{1}H NMR (400 MHz, CDCl3): δ 7.54–7.52 (m, 4 H), 7.39–7.35 (m, 4 H), 7.29–7.25 (m, 2 H), 7.13 (s, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 137.4, 128.71, 128.70, 127.6, 126.5; IR (neat): 3076 (w), 3058 (w), 3019 (w), 2997 (w), 1947 (w), 1878 (w), 1817 (w), 1751 (w), 1597 (w), 1577 (w), 1494 (m), 1450 (m), 1389 (w), 1331 (w), 1300 (w), 1220 (w), 1154 (w), 1071 (w), 1028 (w), 983 (w), 960 (m), 909 (w), 761 (m), 690 (m), 619 (w); MS (EI, 70 eV) 181 ($[M+1]^+$, 14)180 ($[M]^+$, 100), 179 (99), 178 (62), 176 (10), 177 (8), 166 (6), 165 (45), 152 (12), 151 (6), 102 (7), 89 (14), 77 (6), 76 (10), 63 (5), 51 (6); TLC (hexane) R_f 0.31.



1.2 equiv 1.0 equiv

13 examples
up to 83% yield

Stereospecific synthesis of (*E*)-stilbene derivatives by palladium-catalyzed Suzuki-Miyaura cross-coupling reaction

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Highlights

- (*E*)-stilbene derivatives were synthesized with complete isomeric purity
- 9-BBN catalyzed the hydroboration of phenyl acetylene with pinacol borane
- (*E*)-2-phenylethenylboronic acid pinacol ester was used as the organometallic donor
- Electron-rich, electron-poor, and hetereoaryl bromides were successfully coupled
- Electron-rich aryl bromides required use of the *t*-Bu_3PHBF_4 ligand