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An efficient palladium-catalyzed Negishi cross-coupling reaction with arylvinyl iodides: facile regioselective synthesis of *E*-stilbenes and their analogues

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Abstract—A general synthetic route for the Pd-catalyzed cross-coupling of an arylzinc reagent with arylvinyl iodides (Negishi cross-coupling) has been developed. The system permits efficient and selective preparation of *E*-stilbenes and their analogues. It also functions effectively at low levels of catalyst loading without the need for an additional ligand and tolerates a wide range of functional groups including heteroaromatic substrates. A systematic study of various parameters was performed and correlated with catalyst–substrate activity.

Palladium-catalyzed cross-coupling reactions of unsaturated organohalides and sulfonates with organometallic reagents are well established and powerful methods for the construction of carbon–carbon bonds.[1] The most widely used Pd-catalyzed cross-coupling reactions, which involve the formation of $C(sp^2)$–$C(sp^2)$ bonds, are couplings between aryl- or vinylhalides with organotin (Stille) or organoborane (Suzuki–Miyaura) reagents;[2] organozinc (Negishi) and organomagnesium (Kumuda) reagents are employed to a lesser extent.

Stilbenoids have been isolated from various plant species and are currently attracting considerable attention because of their wide range of biological activity and potential therapeutic value.[3] In some cases these antimicrobial agents are active against drug resistant strains of tuberculosis and anthrax[3a] and have recently attracted our attention. Classical synthetic approaches to this class of compounds involve Wittig type reactions, dehydration of 1,2 diarylethanols and metal-catalyzed reactions.[4]

In addition to Stille and Suzuki–Miyaura couplings, Pd-catalyzed Mizoroki–Heck reactions between styrene and arylhalide are well-known processes for the synthesis of stilbenes, albeit with less regioselectivity. The latter reaction produces mixtures of three products: *Z*- and *E*-stilbenes and a coupled product with exocyclic carbon–carbon double bonds (1,1-diphenylethylene).[4] The regiochemistry of the Mizoroki–Heck reaction can be controlled in some cases by careful choice of reaction conditions and, more importantly, by crucial choice of a supporting ligand.[5] Despite the widespread use of boronic acids in Suzuki–Miyaura cross-couplings and the advantages associated with these reagents, difficulties still remain.[6] Problems include the frequent need for recrystallization of the arylboronic acid prior to use, the tendency to form varying amounts of boroxines, the propensity to undergo competitive protodeboronation during cross-coupling, as well as the preparation and application of hindered boronic acids. In addition to these problems, the presence of either electron donating or withdrawing groups may reduce the stability of the arylboronic acid. The lesser reactivity of aryltin (Stille coupling) reagents requires the use of highly polar solvents and harsh reaction conditions, in addition to the well-known toxicity of organotin compounds.[7]

In cases where the aforementioned problems exist in traditional metal-catalyzed reactions, a potential solution would be to employ an alternative nucleophilic partner

Keywords: Negishi cross-coupling; Regioselective synthesis of *E*-stilbenes; Arylvinyl iodides; Metal-catalyzed one-pot synthesis.
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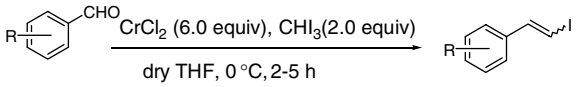
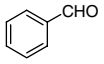
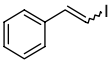
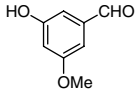
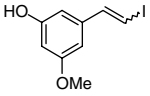
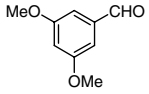
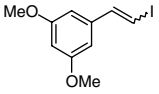
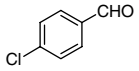
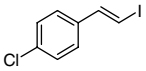
Table 1. Preparation of arylvinyl iodides under optimized conditions



Entry	Aldehydes	Arylvinyl iodides	Time (h)	Yield (%)	E/Z[a]
1			2.5	87	94:6
2			3.0	92	94:6
3			5.0	84	92:8
4			2.5	82	100:0

[a] E/Z ratio was determined by analysis of the ^{1}H NMR spectrum of the crude material.

such as an arylzinc reagent. Recently, a simple procedure has been developed to prepare arylvinyl iodides (electrophilic partners) in high yield and excellent regioselectivity based on the adaptation of a reported procedure (Table 1, entries 1–4).[8]

Since a facile preparation of the arylvinyl iodides was in hand, it was decided to use them with the aforementioned arylzinc reagents to prepare functionalized stilbenes and their analogues.

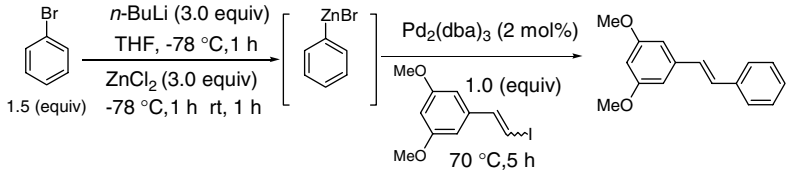
To these authors' knowledge, previously there has been no report of a general efficient Pd-catalyzed Negishi cross-coupling reaction for the regioselective synthesis of *E*-stilbenes and their analogues from arylvinylhalides, except for the preparation of a *Z*-stilbene from a *Z*-arylvinyl bromide.[9]

Herein we report a simple and general procedure for the preparation of the *E*-stilbene class of compounds from arylvinyl iodides employing a Pd-catalyzed Negishi protocol.

Several features of this method are noteworthy. First, easy access to various arylvinyl iodides with excellent regioselectivity (Table 1, entries 1–4) is available.[10] Second and most importantly, mixtures of *E*- and *Z*-isomers of arylvinyl iodides gave only regioselective *E*-stilbenes. Unlike the Heck reaction, wherein a mixture of isomeric arylvinyl coupled products is formed (i.e., *Z*-, *E*-, and exocyclic isomers),[4] only the *E*-isomer is observed with this process.[10] Third, low levels of catalyst loading (2 mol %) with no additional ligand and no co-solvent is required for these transformations. Fourth, nucleophilic partners such as arylzinc reagents gave coupled products at moderate (rt to 70 °C) reaction temperatures. In addition to the above, the present method gives better yields for heterocyclic stilbene analogues than previously reported.[4d,11,12]

Initial studies indicated that the coupling of an arylvinyl iodide with an arylzinc reagent in the presence of $Pd(PPh_3)_4$ gave only the corresponding *E*-regioisomer of the stilbene (Table 2, entry 3). The arylzinc reagents were typically prepared from their corresponding

Table 2. Effect of reaction conditions on the yields of aryl–arylvinyl one-pot Negishi couplings



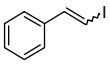
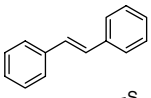
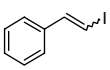
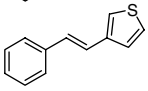
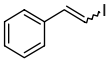
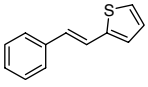
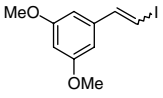
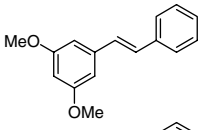
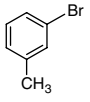
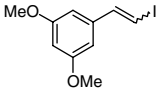
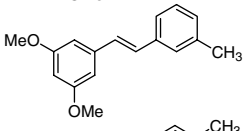
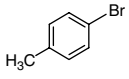
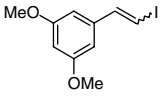
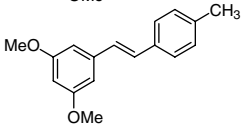
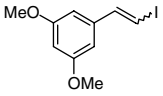
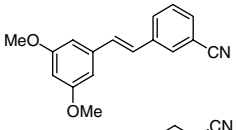
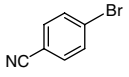
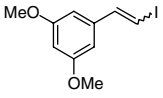
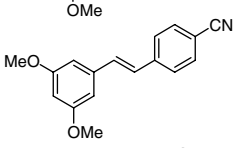
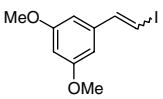
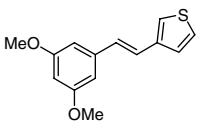
Entry	Change from standard conditions	Yield (%)
1	None	74
2	No $Pd_2(dba)_3$	0
3	$Pd(PPh_3)_4$	62
4	$Pd_2(dba)_3$ and $P(Cy)_3$	72
5	Cosolvent (THF/NMP; 2:1)	33
6	DMF	0
7	DMA	0

arylbromides. Halogen-lithium exchange followed by transmetallation with anhydrous Zn(II)chloride furnished the desired arylzinc reagent. Subsequent reaction with an arylvinyl iodide in the presence of $Pd_2(dba)_3$ catalyst gave the cross-coupled product. The $Pd_2(dba)_3$ was a more effective catalyst than $Pd(PPh_3)_4$ (Table 2, entries 1 and 3). As expected, no cross-coupled product was observed in the absence of the $Pd_2(dba)_3$ catalyst (Table 2, entry 2). Alternatively, no substantial increase in yield was observed when $Pd_2(dba)_3$ was used with the ligand $P(Cy)_3$ (Table 2, entry 4). The use of polar solvents (Table 2, entries 6 and 7) led to an aryl acetylene for β-hydride elimination occurred and no cross-coupled product was observed. Use of the cosolvent NMP with THF also gave significant amounts of aryl acetylene (>30%), along with a low yield of the cross-coupled product (33%; Table 2, entry 5).

As a result of this study, the standard conditions, as exhibited in entry 1 of Table 2, were chosen to further investigate substrate scope and reactivity of this process.

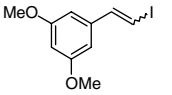
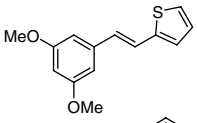
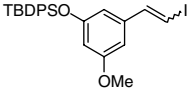
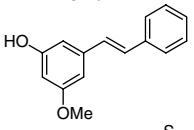
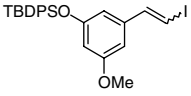
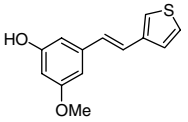
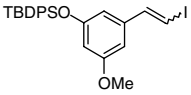
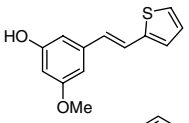
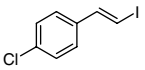
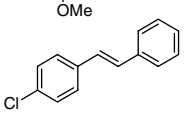
Examination of the data in Table 3 demonstrates that the use of $Pd_2(dba)_3$ in THF at either rt or 70 °C provided good to excellent yields of stilbenes in the presence of a variety of common functional groups, including cyano, alkoxy, TBDPS, halide, and alkyl substituents. The reaction occurred efficiently at low levels of catalyst loading (2 mol %) without any supporting ligand. Heteroarylzinc reagents gave cross-coupled products at room temperature in 2 h with excellent yields (>80%, Table 3, entries 2, 3, 9, 10, 12, and 13). No aryl acetylene which would originate from β-hydride elimination[13] was observed in these processes. In contrast to heteroarylzinc reagents, conventional arylzinc reagents gave slightly lower yields (65–78%, Table 3, entries 1, 4–8, 11, and 14) and required higher temperatures of 70 °C over a 3–5 h period. Variations in electronic character (Table 3, entries 5–8) gave no noticeable change in yields. A small amount of aryl acetylene (~5–10%) was observed in reactions using conventional arylzinc reagents at higher temperatures. Cross-coupling between hydroxy-substituted arylvinyl iodides and an arylzinc reagent did not proceed without protection of the hydroxyl group (Table 3, entries 11–13). Despite the need for protection of hydroxy-substituted arylvinyl iodides, the cross-coupling and deprotection steps can be accomplished efficiently in a one-pot process, as expected (Scheme 1).

Table 3. Pd-catalyzed Negishi cross-coupling reactions of arylvinyl iodides with arylzinc reagents[a]

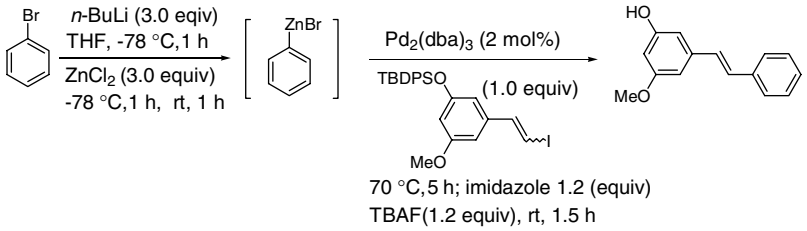
Entry	Arylbromide	Arylvinyl iodides	*E*-stilbenes	Temp (°C)	Time (h)	Yield[b] (%)
1				70	3	78
2				rt	2	86[c]
3				rt	2	81[c]
4				70	5	74
5				70	5	63
6				70	5	72
7				70	5	70
8				70	5	61
9				rt	2	88[c]

(*continued on next page*)

Table 3 (*continued*)

Entry	Arylbromide	Arylvinyl iodides	*E*-stilbenes	Temp (°C)	Time (h)	Yield[b] (%)
10				rt	2	84[c]
11				70	5	73
12				rt	5	82[c]
13				rt	5	84[c]
14				70	5	65

[a] All reactions are carried out in dry THF; ArBr/*n*-BuLi/$ZnCl_2$/Arylvinyliodide/$Pd_2(dba)_3$ = 1.5:3.0:4.0:1.0:0.02.
[b] Isolated yield based on the amount of arylvinyl iodide.
[c] No aryl acetylene from β-hydride elimination was observed.



Scheme 1. One-pot Negishi coupling of protected arylvinyl iodide–arylzinc reagents, followed by deprotection with TBAF.

Since only full conversion of the arylvinyl iodide gave the highest yields of cross-coupled product, the best condition which was found, employed was a slight excess of arylbromide (1.5 equiv) in the presence of 3.0 equiv of *n*-BuLi. Preliminary work indicated consistent formation of a small amount of homocoupled product (<5–10%), which was initially difficult to remove from some reaction mixtures. It became apparent that the initial use of 1.2 equiv of aryl bromide did not permit full conversion of the arylvinyl iodides to the cross-coupled products. The use of an excess amount of arylbromide (1.5 equiv) provided full conversion, which maximized the yield of cross-coupled product and simplified the removal of unwanted homocoupled product from the reaction mixtures.

Interestingly, a simple control reaction with the arylvinyl iodide and $Pd_2(dba)_3$ in THF at rt (stirred overnight) also gave the aforementioned aryl acetylene in approximately 20% yield. This result, in addition to the insights gained earlier (cf. Table 3, entries 2, 3, 9, 10, 12, and 13), revealed that lower temperature and decreased reaction times, as well as the order of the addition of reagents decreased the amount of aryl acetylene byproduct. Since this optimization improved the yield and minimized the formation of aryl acetylene, it was applied to further reaction processes (Table 3). Indeed, it was found that addition of the $Pd_2(dba)_3$ catalyst should be done initially, followed by rapid addition of the arylvinyl iodide, and then immediately placing the reaction flask in a preheated oil bath (70 °C) provided the best yields of the stilbenes.[14]

In summary, a simple and general procedure for the construction of $C(sp^2)$–$C(sp^2)$ bonds from arylvinyl iodides and arylzinc reagents has been developed. The process was applied to the preparation of many stilbenes and their analogues which have antimicrobial activity.[10] The system is very simple, effective and cheap when compared to other Negishi cross-coupling reactions. With respect to turnover numbers for competing reactions of arylbromides and arylvinyl iodides, this process has a much higher turnover number. Ready access to versatile arylvinyl iodides should facilitate the further development in the formation of $C(sp^2)$–$C(sp^2)$ bonds using Negishi cross-coupling protocols.

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References and notes

1. (a) Kataoka, N.; Shelby, Q.; Stambuli, J. P.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 5553; (b) *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; John Wiley & Sons: New York, 2002; (c) *Organometallics in Organic Synthesis*; Negishi, E., Ed.; John Wiley & Sons: New York, 1980; (d) *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: New York, 1998.
2. (a) Hasan, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemarie, M. *Chem. Rev.* **2002**, *102*, 1359; (b) Littkle, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176; (c) Lessene, G. *Aust. J. Chem.* **2004**, 57.
3. (a) Monte, A.; Rott, M.; Defoe, L.; Schwan, W. R. U.S. Patent Appl. Publ. 2006, 26; (b) Sanghee, K.; Hyojin, K.; Jae, E. P.; Sungkyu, J.; Sang, K. L.; Young-Jin, C. *J. Med. Chem.* **2002**, *45*, 160; (c) Aggarwal, B. B.; Bhardwaj, A.; Aggarwal, R. S.; Seeram, N. P.; Shishodia, S.; Takada, Y. *Anticancer Res.* **2004**, *24*, 2783; (d) Wolter, F.; Stein, J. *Drugs Future* **2002**, *27*, 949; (e) Fremont, L. *Life Sci.* **2000**, *66*, 663; (f) Jang, M.; Cai, E. N.; Udeani, G. O.; Slowing, K. V.; Thomas, C. F.; Beecher, C. W. W.; Fong, H. S.; Farnsworth, N. R.; Kinghorn, A. D.; Metha, R. G.; Moon, R. C.; Pezzuto, J. M. *Science* **1997**, *275*, 218; (g) *The Biochemistry of the Stilbenoids*; Gorham, J., Ed.; Chapman & Hall: London, 1995; (h) Bradamante, S.; Barenghi, L.; Villa, A. *Cardiovasc. Drug Rev.* **2004**, *22*, 169; (i) Belovsky, G.; Percivill, D.; Lewis, K.; Tegos, G. P.; Ekart, J. *J. Nat. Prod.* **2004**, *67*, 481.
4. (a) Ferre-Filmon, K.; Delaude, L.; Demonceau, A.; Noels, A. F. *Coord. Chem. Rev.* **2004**, *248*, 2323; (b) Reetz, M. T.; Lohmer, G.; Lohmer, R.; Westermann, E. Ger. Offen. 2000, DE 19843012; (c) Alonso, E.; Ramon, D. J.; Yus, M. *J. Org. Chem.* **1997**, *62*, 417; (d) Molander, G. A.; Bernardi, C. R. *J. Org. Chem.* **2002**, *67*, 8424.
5. (a) Tietze, L. F.; Nordmann, G. *Synlett* **2001**, 337; (b) Maddux, T.; Li, W.; Yu, L. *J. Am. Chem. Soc.* **1997**, *119*, 844; (c) Sengupta, S.; Sadhukhan, S. K.; Singh, R. S.; Pal, N. *Tetrahedron Lett.* **2002**, *43*, 1117; (d) Belfield, K. D.; Chinna, C.; Schaffer *Tetrahedron Lett.* **1997**, 6131; (e) Guiso, M.; Marra, C.; Farina, A. *Tetrahedron Lett.* **2002**, *43*, 597; (f) Thomas, N. F.; Lee, K. C.; Paraidathathu, T.; Weber, J. F. F.; Awang, K.; Rondeau, D.; Richomme, P. *Tetrahedron* **2002**, *58*, 7201; (g) Beller, M.; Zapf, A. *Synlett* **1998**, 792; (h) Reetz, M. T.; Lohmer, G.; Schwickardi, R. *Angew. Chem., Int. Ed.* **1998**, *37*, 481.
6. (a) Jacqueline, E. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 13028; (b) Handy, S. T.; Zhang, Y.; Bergman, H. *J. Org. Chem.* **2004**, *69*, 2362; (c) Chaumeil, H.; Signorella, S.; Le Drian, C. *Tetrahedron* **2000**, *56*, 9655; (d) Watanabe, T.; Miyaura, N.; Suzuki, A. *Synlett* **1992**, 207.
7. (a) Sander, H. L. T.; Deelman, B. J.; Koten, G. V. *J. Organomet. Chem.* **2004**, *689*, 2145; (b) Kimbrough, R. D. *Environ. Health Perspect.* **1976**, *14*, 51.
8. Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408.
9. Bosanac, T.; Wilcox, C. S. *Tetrahedron Lett.* **2001**, *42*, 4309.
10. Cook, J. M.; Defoe, L.; Kabir, M. S.; Monte, A.; Rott, M.; Schwan, W. R. US CIP Anti-Infective Agents and Methods of Use, Application 04/06/2007.
11. Heynekamp, J. J.; Weber, W. M.; Hunsaker, L. A.; Gonzales, A. M.; Orlando, R. A.; Deck, L. M.; Vander Jagt, D. L. *J. Med. Chem.* **2006**, *49*, 7182.
12. (a) Botella, L.; Carmen, N. *Tetrahedron* **2004**, *60*, 5563; (b) Velder, J.; Ritter, S.; Lex, J.; Schmalz, H.-G. *Synthesis* **2006**, 273.
13. Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 12527.
14. *Typical procedure*: *Pd-catalyzed Negishi cross-couplings of aryl halides and arylvinyl iodides*. An oven dried round bottomed flask containing a magnetic stir bar was sealed with a rubber septum and then evacuated and backfilled with argon (the sequence was repeated three times) while cooling. The round bottomed flask was then charged with arylbromide (1.5 equiv) and dry THF (2 mL). The solution which resulted was cooled to −78 °C and then *n*-BuLi (2.5 M in hexanes 3.0 equiv) was added via a syringe through the septum, and the solution which resulted was stirred at −78 °C for 1 h. The dry $ZnCl_2$ (3.0 equiv) was then added in one solid portion by removal of the septum at −78 °C. The mixture which resulted was stirred for 1 h at −78 °C and the flask was removed from the cooling bath and stirred at room temperature for 1 h. The $Pd_2(dba)_3$ (2 mol %) catalyst was added to the reaction mixture in one solid portion by removal of the septum and this was followed by rapid addition of the arylvinyl iodide in THF via a syringe through the resealed septum. A previously flame dried reflux condenser was used to cap the reaction flask and the top of the condenser was sealed with a septum and teflon. The reaction was kept under an argon atmosphere. The reaction mixture was immediately placed in a preheated oil bath at 70 °C and stirred (magnetic stir) for 3–5 h or stirred at room temperature for 2–3 h depending on the substrates until the arylvinyl iodide had been completely consumed as indicated by examination of a sample of the crude reaction mixture by ^1H NMR spectroscopy. The reaction mixture was then cooled to rt, diluted with water (4 mL), and extracted with diethylether (4 × 10 mL). The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel to give the pure cross-coupled product (see Table 3 for yields).