Organic Syntheses

A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

The procedures described in *Organic Syntheses* are provided as published and are conducted at one's own risk. *Organic Syntheses, Inc.*, its Editors, and its Board of Directors do not warrant or guarantee the safety of individuals using these procedures and hereby disclaim any liability for any injuries or damages claimed to have resulted from or related in any way to the procedures herein.

September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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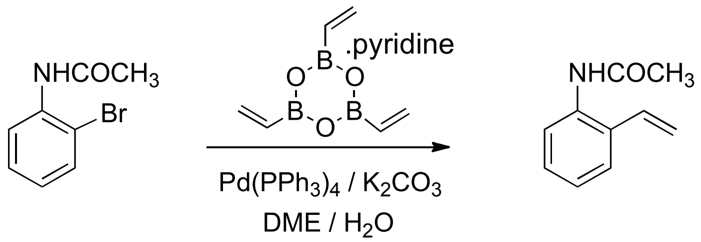
Discussion Addendum for: Suzuki-Miyaura Cross-Coupling: Preparation of 2'-Vinylacetanilide



Prepared by Donal F. O'Shea.*[1]
Original article: Cottineau, B.; Kessler, A.; O'Shea, D. F. *Org. Synth.* **2006**, *83*, 45.

Functionalized styrenes are of considerable importance as versatile synthetic intermediates and for the generation of new polymeric materials. The diverse spectrum of transformations achievable from the two carbon unit of the vinyl functional group has given rise to the development of numerous approaches for their synthesis.[2] Some of the more salient features of any reagent are bench-stability, a general set of reaction conditions in which it can be employed and substrate functional group tolerance. At the outset we felt an attractive approach to achieving vinylations would be to utilize a Suzuki-Miyaura cross coupling protocol which would necessitate a vinyl boronic acid reagent. But an immediate stumbling block to this approach was the instability of vinyl boronic acid which undergoes polymerization upon attempted isolation.[3a,c] Consequently to address this issue we turned to a pyridine promoted cyclotrimerization as an atom economical approach to stabilizing vinyl boronic acid as its trivinylboroxane-pyridine complex (Figure 1).[3a,b] While the trivinylboroxane is a bench stable solid, under the aqueous basic conditions of a Suzuki-Miyaura cross coupling it can hydrolyze to the vinyl boronic acid *in situ*.[3a] Since our initial report on use of this reagent it has become commercially available from several vendors and has been successfully exploited for C-C, C-O and C-N bond forming transformations.

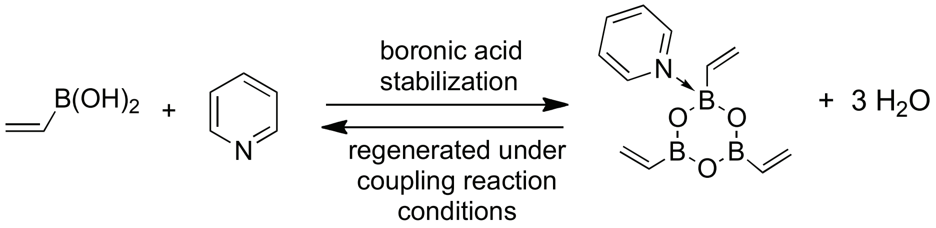
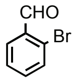
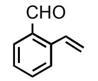
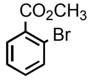
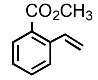
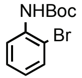
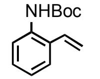
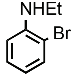
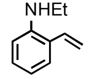
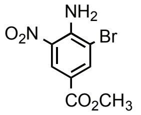
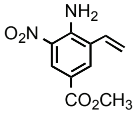
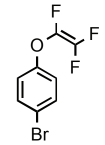
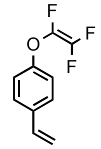
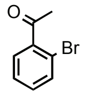
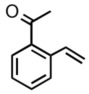
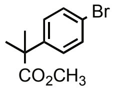
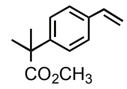
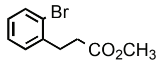
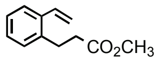
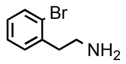
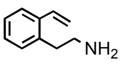
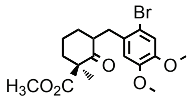
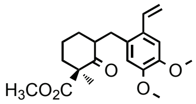
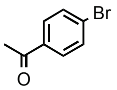
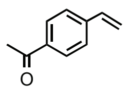
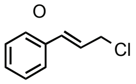
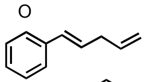
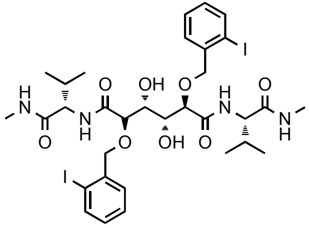
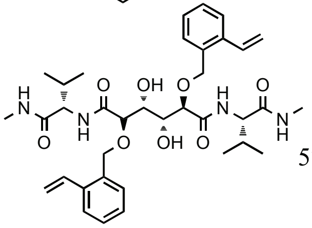
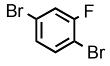
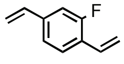
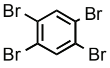
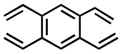
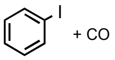
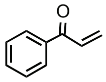


Figure 1. Stabilization of vinyl boronic acid and *in situ* reaction regeneration.

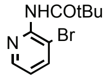
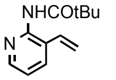
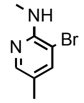
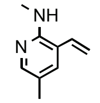
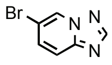
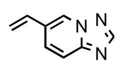
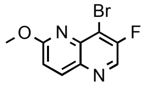
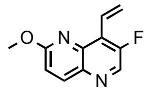
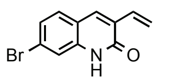
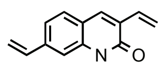
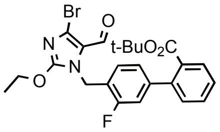
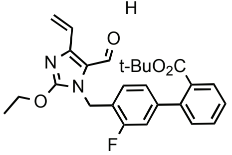
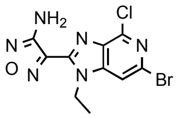
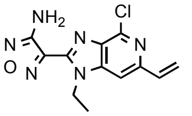
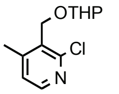
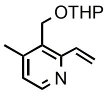
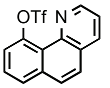
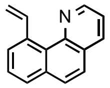
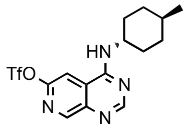
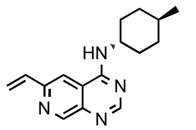
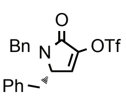
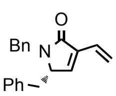
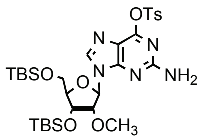
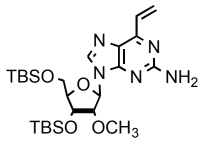
Vinylation of arenes with trivinylboroxane has been reported for a diverse range of *ortho*- *meta*- and *para*- substituted aryl rings (Table 1). The coupling reaction has shown an impressive range of functional group tolerance with good yields for many electronically and sterically challenging substrates. In the majority of examples the arylbromide substrate was utilized in conjunction with our general set of reaction conditions of $Pd(PPh_3)_4$ as catalyst and a carbonate base with dimethoxyethane / water as solvent (Table 1, entries 1-11). In several cases the trivinylboroxane was used in a 0.5 equiv. ratio to the coupling substrate illustrating that the vinyl-trimer can hydrolyze *in situ* to generate three equiv. of vinyl boronic acid.[5,18] It was shown that a recoverable polymer bound palladacycle could be used for vinylation reactions of aryl bromides (Table 1, entry 12) in addition to coupling of cinnamyl- and benzyl-chloride to provide 1-phenylpenta-1,4-diene and allylbenzene respectively (Table 1, entry 13). Multiple vinylations of substrates have also been accomplished with this reagent. For example, the di-vinylation of two different aryl rings of a HIV-1 protease inhibitor substrate (Table 1, entry 14) and of 1,4-dibromo-2-fluorobenzene were successfully accomplished (Table 1, entry 15). Remarkably, a tetra-vinylation provided 1,2,4,5-tetravinylbenzene in almost quantitative yields from the corresponding tetrabromobenzene (Table 1, entry 16). The palladium-catalyzed carbonylative cross-coupling of iodobenzene with 0.34 equiv. of trivinylboroxane gave phenylpropenone illustrating that each vinyl moiety of the reagent is available for reaction in this transformation (Table 1, entry 17).

Table 1. Representative examples of aryl, allyl and carbonylative vinylations.

Entry	Substrate	Product	Yield	Conditions
1[3a]			93%	$Pd(PPh_3)_4$, K_2CO_3, DME / H_2O, reflux, 15h
2[3a]			91%	$Pd(PPh_3)_4$, K_2CO_3, DME / H_2O, reflux, 15h
3[4]			90%	$Pd(PPh_3)_4$, K_2CO_3, DME / H_2O, reflux, 20h
4[5]			78%	$Pd(PPh_3)_4$, K_2CO_3, DME / H_2O, reflux, 20h
5[6]			77%	$Pd(PPh_3)_4$, K_2CO_3, DME / H_2O, reflux, 3h
6[7]			74%	$Pd(PPh_3)_4$, K_2CO_3, DME / H_2O, reflux, 20h
7[8]			95%	$Pd(PPh_3)_4$, K_2CO_3, DME / H_2O, reflux, 14h
8[9]			70%	$Pd(PPh_3)_4$, K_2CO_3, DME / H_2O, microwave, 130 °C, 1h
9[10]			78%	$Pd(PPh_3)_4$, K_2CO_3, DME / H_2O, reflux, 20h
10[11]			86%	$Pd(PPh_3)_4$, K_2CO_3, DME / H_2O, reflux, 20h
11[12]			70%	$Pd(PPh_3)_4$, K_2CO_3, DME / H_2O, reflux, 24h
12[13]			88%	PS-Pd, TBAB, K_2CO_3, H_2O, 100 °C, 2.5h
13[13]			80%	PS-Pd, TBAB, KOH, H_2O-acetone, 50 °C, 2.5h
14[14]			57%	$Pd(OAc)_2$, $[(tBu_3)PH]BF_4$, K_2CO_3, DME / H_2O, microwave, 100 °C, 15 min
15[15]			56%	$Pd(PPh_3)_4$, K_2CO_3, DME / H_2O, 85 °C, 24 h
16[16]			99%	$Pd(OAc)_2$, PPh_3 K_2CO_3, DME / H_2O, 100 °C, autoclave, 24h
17[17]			67%	P_{CO} 5 bar, $Pd(OAc)_2$, Ph_3P, THF, 80 °C, 20 h

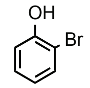
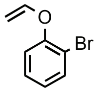
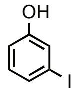
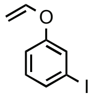
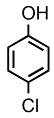
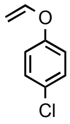
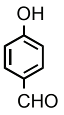
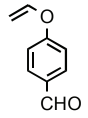
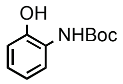
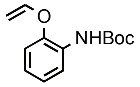
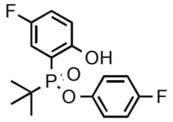
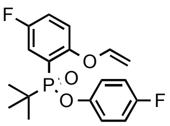
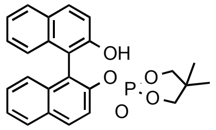
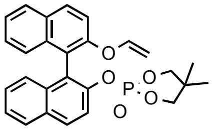
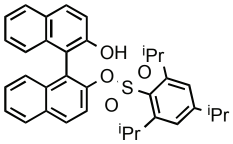
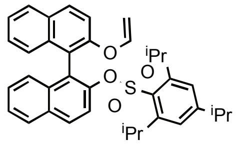
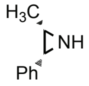
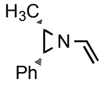
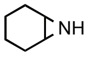
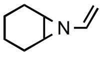
Cross-coupling of heterocycles has also been extensively employed with the vinylboroxane reagent. Again, a uniformity of reaction conditions has been used across a diverse range of substrates often providing the products in excellent yields (Table 2). In addition to bromo-substituted heterocycles (entries 1-7), chloro (entry 8), triflate (entries 9-11) and tosylate (entry 12) derivatives have been successfully utilized as coupling partners.

Table 2. Representative examples of heterocycle vinylations.

Entry	Substrate	Product	Yield	Conditions
1[18]			85%	Pd(PPh_3)$_4$, K_2CO_3, DME / H_2O, reflux, 20 h
2[18]			86%	Pd(PPh_3)$_4$, K_2CO_3, DME / H_2O, reflux, 20 h
3[19]			93%	Pd(PPh_3)$_4$, K_2CO_3, DME / H_2O, reflux, 24 h
4[20]			90%	Pd(PPh_3)$_4$, K_2CO_3, DME / H_2O, 85 °C ,10 h
5[21]			88%	Pd(PPh_3)$_4$, Na_2CO_3, THF / H_2O, 70 °C, 12 h
6[22]			76%	Pd(PPh_3)$_4$, K_2CO_3, DME / H_2O, 85 °C, 2 h
7[23]			95%	Pd(PPh_3)$_4$, K_2CO_3, dioxane / H_2O, 75 °C
8[24]			89%	Pd(PPh_3)$_4$, K_2CO_3, DME / H_2O, reflux, 20 h
9[25]			76%	Pd(PPh_3)$_4$, K_2CO_3, DME / H_2O, reflux, 17 h
10[26]			71%	Pd(PPh_3)$_4$, K_2CO_3, DME / H_2O, microwave 150 °C, 30 min
11[27]			78%	Pd(PPh_3)$_4$, Na_2CO_3, dioxane / H_2O, microwave 90 °C, 5 min
12[28]			not reported	Pd(PPh_3)$_4$, LiBr, dioxane / H_2O

The scope of transformations utilizing this reagent has been broadened with both *O*-vinylation and *N*-vinylation methods reported (Table 3). Coupling conditions were mediated by copper acetate for both *O* and *N* heteroatoms at room temperature using CH_2Cl_2/pyridine as solvent system.[29] These mild conditions were tolerant of halo (entries 1-3), formyl (entry 4), phosphinate (entry 6) and aziridine (entries 9, 10) functional groups.

Table 3. Representative examples of *O* and *N* vinylations.

Entry	Substrate	Product	Yield	Conditions
1[29]			95%	$Cu(OAc)_2$, pyridine, CH_2Cl_2, rt, 24 h
2[29]			76%	$Cu(OAc)_2$, pyridine, CH_2Cl_2, rt, 24 h
3[29]			76%	$Cu(OAc)_2$, pyridine, CH_2Cl_2, rt, 24 h
4[29]			84%	$Cu(OAc)_2$, pyridine, CH_2Cl_2, rt, 24 h
5[30]			52%	$Cu(OAc)_2$, pyridine, CH_2Cl_2, rt, 24 h
6[31]			71%	$Cu(OAc)_2$, pyridine, CH_2Cl_2, O_2, rt, 40 h
7[32]			77%	$Cu(OAc)_2$, pyridine, CH_2Cl_2, O_2, rt, 40 h
8[32]			71%	$Cu(OAc)_2$, pyridine, CH_2Cl_2, O_2, rt, 40 h
9[33]			30%	$Cu(OAc)_2$, myristic acid, 2,6-lutidine, toluene, rt, 24 h
10[34]			27%	$Cu(OAc)_2$, pyridine, O_2, rt, 10 h

In summary, 2,4,6-trivinylcyclotriboroxane-pyridine complex continues to serve as a versatile and reliable vinyl source for a range of important coupling reactions.

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Donal O'Shea received his Ph.D. degree in Chemistry from University College Galway (Ireland) in 1994. He held post-doctoral positions in the University of Edinburgh (Scotland) and Carnegie Mellon University, Pittsburgh (USA) following which he was a research scientist at Eastman Kodak Company in Rochester, New York. In 1999 he returned to academia to a position in University College Dublin and was promoted to Associate Professor of Chemistry in 2007. His current research interests include development of new synthetic strategies utilizing mixed Li/K metal amides, automated flow micro-reactors, the development of light activated therapeutics and near-infrared fluorochromes.