Communications

Scope and Limitations of the Palladium-Catalyzed Cross-Coupling Reaction of in Situ Generated Organoboranes with Aryl and Vinyl Halides

Shawn P. Maddaford and Brian A. Keay*

Department of Chemistry, University of Calgary, Calgary, Alberta, Canada T2N 1N4

Summary: The in situ palladium(0)-catalyzed Suzuki reaction is shown to be an efficient method for the cross-coupling of aryl-, furyl-, primary, and benzylic boranes with aryl or vinyl bromides and iodides without the isolation of the organoboronic acid or the addition of any external base.

In our previous attempts to apply the Stille-type cross-coupling of (tri-n-butylstannyl)furan 2 with aryl bromides, we observed low yields of cross-coupled products (<50% yields), and no reaction was observed with vinyl halides, 2-bromopyridine, or 1-bromo-2-methoxybenzene (Scheme 1).[1] In contrast to the Stille couplings of 2, the corresponding 4-lithiofuran 1, when treated with trimethoxyborane (B(OMe)₃) followed by a palladium catalyst and water (no external base), cleanly underwent an in situ Suzuki cross coupling with a variety of aryl and vinyl halides and triflates.[2] Since previous successful Suzuki cross-couplings of alkyl-,[3] vinyl-,[4] and arylboronic[5]

Scheme 1

1 R = R₁ = Li
2 R = Sn(Bu)₃, R₁ = H
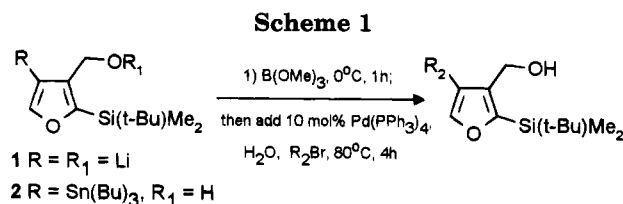
acids with alkyl, vinyl, and aryl halides and triflates required the isolation of the boronic acids and addition of external bases such as hydroxide, ethoxide, or carbonate we decided to investigate our modified in situ Suzuki reaction in detail to determine the scope and limitations of the reaction.

In order to optimize the reaction conditions, the palladium cross-coupling of a phenylborane[6] (generated in situ) with either bromobenzene or iodobenzene to produce biphenyl was examined (Table 1).[7] The addition of water to the reaction mixture after the addition of the B(OMe)₃ resulted in an increased yield of biphenyl (compare entries 12 and 13). The increased yield in the presence of water may be due to an in situ hydroylsis of the

® Abstract published in Advance ACS Abstracts, October 15, 1994.

(1) Keay, B. A.; Bontront, J. J. Can. J. Chem. 1991, 69, 1326.

(2) (a) Cristofoli, W. A.; Keay, B. A. Tetrahedron Lett. 1991, 32, 5881. (b) Cristofoli, W. A.; Keay, B. A. Synlett 1994, 625. Since the appearance of our initial paper in 1991, Friesen et al. have reported a successful use of our in situ Suzuki reaction: Friesen, R. W.; Loo, R. W.; Sturino, C. F. Can. J. Chem. 1994, 72, 1262.

(3) (a) Waas, J. R.; Sidduri, A.; Knochel, P. Tetrahedron Lett. 1992, 26, 3717. (b) Ishiyama, T.; Abe, S.; Miyaura, N.; Suzuki, A. Chem. Lett. 1992, 691 and references therein.

(4) (a) Ishiyama, T.; Miyaura, N.; Suzuki, A. Chem. Lett. 1987, 25 and references therein. (b) A palladium-catalyzed cross-coupling involving the use of isolated furyl boroxines has been reported by Wong et al.: Song, Z. Z.; Ho, M. S.; Wong, H. N. C. J. Org. Chem. 1994, 59, 3917 and references therein.

(5) (a) Fu, J.-M.; Zhao B.-P.; Sharp, M. J.; Snieckus, V. Can. J. Chem. 1994, 72, 227 and references therein. (b) Washburn, R. M.; Leven, E.; Albright, C. F.; Billig, F. A.; Cernak, E. S. Adv. Chem. Ser. 1959, 23, 102. (c) Miyaura, N.; Yanagi, T.; Suzuki, A. Synth. Commun. 1981, 11, 513.

(6) Since we do not know (at this time) the structure of the boron compound undergoing the palladium-catalyzed cross-coupling, we will refer to the compound(s) in situ as some type of organoborane.

(7) A typical experimental procedure is exemplified by entry 5, Table 2. To a −78 °C solution of N,N-diisopropylbenzamide (523 mg, 2.55 mmol), THF (9 mL), and TMEDA (1.1 equiv, 0.42 mL) under N₂ was added s-butyllithium (1.1 equiv). Trimethoxyborane (1.3 equiv) was added after 20 min, and the solution was warmed to 0 °C and stirred 1.2 h. The solvent was evaporated, and benzene (9 mL), 2 M aqueous sodium carbonate (2.5 mL, 2 equiv), Pd(PPh₃)₄ (3 mol %, 90 mg), and bromobenzene (1.3 equiv) were added. The mixture was submersed in a preheated oil bath (110 °C), refluxed for 6 h, cooled, and poured into a separatory funnel. The aqueous layer was removed and the organic phase filtered through silica gel (ethyl acetate eluent). The solvent was evaporated to give a yellow oil which was purified by chromatography on silica gel (8:1 hexanes:ethyl acetate) to afford a solid (0.68 g, 95%).

Table 1. Various Attempts To Optimize the Yield of Biphenyl via the *in Situ* Suzuki Cross-Coupling Reaction

entry	solvent	PhX	water or base	catalyst	time (h)	yield[a] of biphenyl (%)
1	DME	I	Na_2CO_3	$Pd(PPh_3)_4$	20	68
2	DME	I	Na_2CO_3	$Pd(PPh_3)_4$	2	53
3[b]	benzene	I	Na_2CO_3	$Pd(PPh_3)_4$	16	61[c]
4[b]	benzene	I	H_2O	$Pd(PPh_3)_4$	16	51[d]
5[b]	benzene	I	Na_2CO_3	$Pd(OAc)_2(PPh_3)_2$	20	85
6	NMP	Br	H_2O	$Pd(PPh_3)_4$	17	63
7	DME	Br	H_2O	$Pd(PPh_3)_4$	1.5	62
8	DME	Br	H_2O/TMEDA[e]	$Pd(PPh_3)_4$	1.5	59
9	DME	Br	Na_2CO_3	$Pd(OAc)_2(PPh_3)_2$	2	76
10	DME	Br	Na_2CO_3	$Pd(PPh_3)_4$	2	49
11	DME	Br	Na_2CO_3	$Pd(Pfuryl_3)_4$	5	53
12	DME	Br	H_2O	$Pd(Ph_3)_4$	1.5	59
13	DME	Br	none	$Pd(Ph_3)_4$	2	9
14[f]	DME	Br	H_2O	$Pd(Ph_3)_4$	1.75	21

[a] Yield obtained by distillation and NMR analysis of the distillate. [b] Aryllithium generated by halogen−metal change of iodobenzene in ether at −95 °C for 10 min. [c] 16% yield of butylbenzene. [d] 12% yield of butylbenzene. [e] 1.0 equiv of TMEDA was added. [f] Boronic acid prepared from phenylmagnesium chloride.

Table 2. Cross Coupling of *in Situ* Generated Organoboranes with Organo Halides

entry	halide	boronic acid source	catalyst	solvent	water source	time (h)	product (% yield)
1	bromobenzene	**5**	$Pd(PPh_3)_4$	benzene	H_2O	15	**10** (55)
2	iodobenzene	iodobenzene	$Pd(PPh_3)_4$	benzene	2 M Na_2CO_3	20	biphenyl (85)
3	bromobenzene	*n*-BuLi	$Pd(OAc)_2(PPh_3)_2$	THF	H_2O	20	*n*-butylbenzene (52)
4	2-bromobenzaldehyde	benzyllithium	$Pd(PPh_3)_4$	toluene	2 M Na_2CO_3	20	2-benzylbenzaldehyde (83)
5	bromobenzene	**6**	$Pd(PPh_3)_4$	benzene	2 M Na_2CO_3	16	**11** (95)
6	bromobenzene	**7**	$Pd(PPh_3)_4$	THF	H_2O	48	**12** (39)
7	bromobenzene	*s*-BuLi	$Pd(OAc)_2(PPh_3)_2$	benzene	H_2O	16	mixture (<30)
8	**3**	**8**	$Pd(PPh_3)_4$	THF	H_2O	19	**13** (43)
9	**4**	**9**	$Pd(PPh_3)_4$	DME	H_2O	2	**14** (72)

phenyldimethoxyborane to phenyldihyroxyborane and/ or an increase in the basicity of the solution. It is apparent that the addition of external base in the form of sodium carbonate makes little difference in the yield of the reaction (entries 7 and 10). The yield also seems to be relatively independent of the aryl halide (iodo vs bromo) (entries 2 and 10). The aryllithium species was also generated by halogen metal exchange of iodobenzene (ether, 10 min, −95 °C; entries 3−5) and then treated with trimethoxyborane. The same reaction when carried out in the presence of sodium carbonate (entry 3) only gave a slightly higher yield (61% vs 51%) than the reaction without any external base added (entry 4). In addition to the expected biphenyl, *n*-butylbenzene was produced in 12%−16% yields. This is presumably due to the slight excess of *n*-butyllithium added (1.1 equiv) and incomplete halogen−metal exchange. Longer coupling reaction times give slightly higher yields (68%, entry 1).

The use of tris(dibenzylideneacetone)bispalladium(0) (Pd₂dba₃) with tri(2-furyl)phosphine in DME gave no improvement in the yield of biphenyl (entry 11) although the reaction proceeded at room temperature in NMP when Pd(PPh₃)₄ was employed as the catalyst (entry 6).

An improvement in the yield of the reaction was observed when the catalyst was changed from Pd(PPh₃)₄ to bis(triphenylphosphine)palladium(0) generated *in situ* by the reaction of palladium(II) acetate and 2 equiv of triphenylphosphine (entries 5 and 9).[8] This catalyst tends to be more reactive as it is coordinatively less saturated than Pd(PPh₃)₄.

The highest yield of biphenyl was 85% (entry 5) in which the aryllithium species was generated by halogen−metal exchange of iodobenzene with *tert*-butyllithium. This yield compares favorably with the best yield (88%) reported by Suzuki *et al.* for the cross-coupling reaction between phenyldihydroxyborane and bromobenzene in the presence of Pd(PPh₃)₄ (2 M Na₂CO₃).[5c] However, our *in situ* reaction does not require the isolation of the

phenyldihydroxyborane, and therefore, the yield of 85% is for two steps.

The effect of the addition of TMEDA on the yield of the reaction was also investigated. This is of concern when adding B(OMe)₃ to lithio species prepared by methods that employ TMEDA,[5a] since it is known that amines form stable complexes with phenyldihydroxyboranes.[9] Thus, the presence of TMEDA may impede the cross-coupling reaction. Surprisingly, the addition of 1 equiv of TMEDA did not noticeably affect the yield of the reaction (entry 8).[10]

Grignard reagents also serve as convenient precursors for this reaction.[5b] The palladium cross-coupling of the phenylborane derived *in situ* from phenylmagnesium chloride and B(OMe)₃ with bromobenzene produced a 21% yield of biphenyl (entry 14). The reaction, when repeated in the presence of 1 equiv of TMEDA, gave a 24% yield of biphenyl.

The scope and limitation of the *in situ* Suzuki reaction was next examined. Table 2 shows the reactions of *in situ* generated aryl-, furyl-, primary, secondary, and benzylic boranes with various vinyl, aryl, and benzylic halides. In general, arylboranes undergo the cross coupling reaction with aryl halides in high yields (entries 1, 2, and 5). Notable is the coupling of the borane made by *ortho*-metalation of *N,N*-diisopropylbenzamide in the presence of TMEDA with bromobenzene to give **11**[5a] in 95% yield. The MOM ether of *p*-hydroxyanisole was regioselectively lithiated according to Narasimhan to give

(8) Amatore *et al.* have shown that triphenylphosphine quantitatively reduces divalent Pd(OAc)₂ to a Pd(0) species by an intramolecular process within the Pd(OAc)₂(PPh₃)₂ complex. Amatore, C.; Jutand, A.; M'Barki, M. A. *Organometallics* **1992**, *11*, 3009.

(9) Toyota, S.; Oki, M. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 1832 and references therein.

(10) Thompson and Gaudino have reported successful palladium-catalyzed cross-couplings of 5-bromonicotinates with aryldihydroxy-boranes in the presence of 1 equiv of triethylamine under nonaqueous conditions; see: Thompson, W. J.; Gaudino, J. *J. Org. Chem.* **1984**, *49*, 5237.

5.[11] The products from the cross-coupling reaction with bromobenzene were obtained as an inseparable mixture of regioisomers, the major one having the phenyl group *ortho* to the MOM group (55% (**10**):3%; entry 1). The remaining product in the reaction mixture was the starting *p*-methoxy-*O*-(methoxymethyl)phenol **5**. The
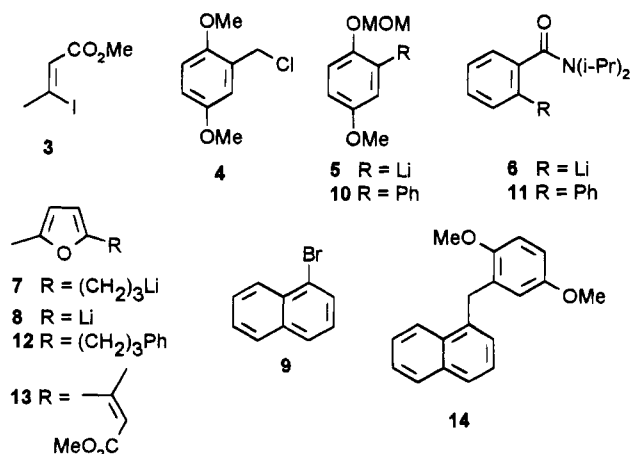
coupling of primary alkylboranes with bromobenzene proceeded in lower yields (entry 3 and 6). The coupling of *n*-butylborane (generated by reaction of *n*-butyllithium with B(OMe)$_3$ at 0 °C) gave a moderate yield of *n*-butylbenzene (52%; entry 3). Other primary boranes are also readily available by halogen–metal exchange of primary iodides with *tert*-butyllithium and trapping with B(OMe)$_3$. Halogen–metal exchange of the corresponding iodide of **7** at −78 °C and trapping of **7** with B(OMe)$_3$, followed by our palladium-catalyzed *in situ* coupling, gave the phenylated product **12** in 39% yield (entry 6). The yield of the reaction was neither improved by the use of Pd(OAc)$_2$(PPh$_3$)$_2$ nor improved by the use of external base. The coupling of *s*-butylborane with bromobenzene using Pd(OAc)$_2$(PPh$_3$)$_2$ gave a mixture of *n*-butyl- and *s*-butylbenzene in low yield (<30%) while Pd(PPh$_3$)$_4$ gave only *n*-butylbenzene. Presumably, the presence *n*-butyl-

benzene arises from the thermal isomerization of the secondary borane to the more stable primary borane.[12] The coupling of 1-naphthylborane with 2,4-dimethoxy-benzyl chloride (**4**) gave **14** in 72% yield (entry 9). The yield of the reaction was not improved by the addition of 2 M Na$_2$CO$_3$.

As furans are easily metalated in the 2- and 5-positions, the 2-(5-methylfuryl)borane species prepared by treating 2-lithio-5-methylfuran (**8**) with B(OMe)$_3$ was coupled with methyl (*E*)-3-iodo-2-butenoate (**3**) to give **13** with the *Z*-geometry in 43% yield (entry 8). The coupling of benzylborane (prepared by the lithiation of toluene in the presence of TMEDA followed by the addition of B(OMe)$_3$)[13] with 2-bromobenzaldehyde gave 2-benzyl-benzaldehyde[14] in 83% yield when 3 equiv of the borane was used (entry 4).

We have shown that the palladium-catalyzed *in situ* Suzuki reaction is indeed of general scope, encompassing a variety of boron-containing organic precursors and tolerating functional groups such as esters, aldehydes, and amides. The method obviates the need for the isolation of the boronic acid, which are often difficult to isolate due to their high water solubility. Conditions which may further better the yields are currently being investigated.

Supplementary Material Available: Experimental procedures and ¹H-NMR and ¹³C-NMR spectra are available for the *in situ* Suzuki reactions (18 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(11) Narasimhan, N. S.; Mali, R. S.; Barve, M. V. *Synthesis* **1979**, 906.

(12) At higher temperatures, secondary alkylboranes can isomerize to place the boron at a primary position. Pelter, A.; Smith, K.; Brown, H. C. *Borane Reagents*; Katrizky, A. R., Meth-Cohn, O., Rees, C. W., Eds.; Academic Press: New York, 1988; p 7.

(13) Wakefield, B. J. *Organolithium Methods*; Academic Press: New York, 1988; p 38.

(14) Arnold, B. J.; Mellows, S. M.; Sammes, P. G.; Wallace, T. W. *J. Chem. Soc., Perkin Trans. 1* **1974**, 401.