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One Pot Biaryl Synthesis *via in situ* Boronate Formation

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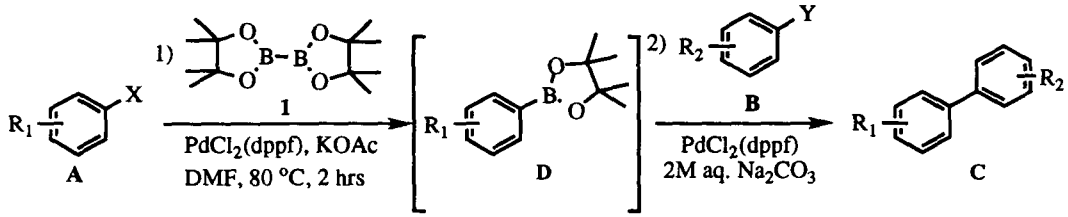
Abstract: The palladium-catalyzed cross-coupling reaction of aryl halides or aryl triflates with diborane **1** yielded structurally diverse aryl boronates which were reacted *in situ* with aryl halides or aryl triflates to afford a variety of biaryls in moderate to high yield. © 1997 Elsevier Science Ltd.

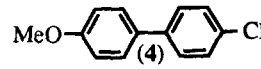
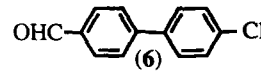
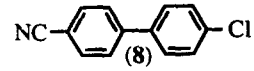
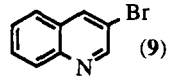
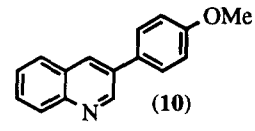
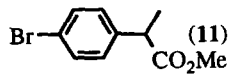
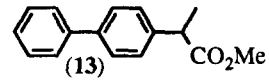
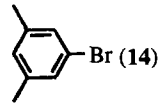
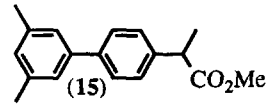
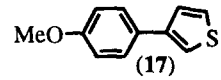
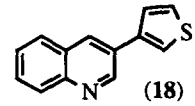
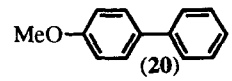
Functionalized unsymmetrical biaryls are widespread in nature[1] and are important constituents of many medicinals.[2] Palladium-catalyzed cross-coupling between aryl boronic acids and haloarenes or aryl triflates has been shown to be a versatile method for the preparation of these biaryls.[3] While several syntheses of boronic acids have been reported, the most popular method is based on the reaction of a trialkyl borate with a Grignard or a lithium reagent.[4] Suzuki, Miyaura, Ishiyama and Matsuda,[5] recently reported the preparation of *cis*-diborylalkenes via the transition-metal-catalyzed addition of tetra-alkoxydiboron **1**[6] to alkynes. This method has been successfully applied to the solid phase synthesis of tetra-substituted ethylenes such as tamoxifen.[7] Moreover the alkoxydiboron **1**, which is thermally stable and easily handled in air, has been shown to be a useful boron nucleophile for the cross-coupling reaction with aryl halides that contain base sensitive functionalities.[8] However, no systematic studies have appeared in the literature regarding the reactivity of these aryl boronates **D**. Herein, we report a method for a one pot preparation of unsymmetrical biaryls *via* a modified *in situ* Suzuki cross-coupling reaction using diborane **1** (Scheme 1).

Scheme 1



X,Y = Br, I, OTf

Table 1. Cross-Coupling of Aryl Halides and Aryl Triflates *via in situ* Formation of an Aryl Boronate.

Entry	Reactant A	Reactant B	Product[a] C	Yield[b] (%)	m.p. °C
a	*p*-$MeOC_6H_4I$ (2)	*p*-ClC_6H_4Br (3)	 (4)	81	110-112[c]
b	3	2		60	
c[d]	*p*-BrC_6H_4CHO (5)	3	 (6)	43	113-114
d	3	5		50	
e	*p*-BrC_6H_4CN (7)	3	 (8)	41	123-125[e]
f	2	 (9)	 (10)	70	85-86[f]
g	 (11)	C_6H_5Br (12)	 (13)	69	colourless oil
h	11	 (14)	 (15)	83	colourless oil
i	2	 (16)	 (17)	80	126-127[g]
j	16	2		34	
k	9	16	 (18)	29	88-89[h]
l	16	9		40	
m	2	Ph-OTf (19)	 (20)	73	84-86[i]
n	19	2		70	

All new compounds were fully characterized and all analytical and spectral (IR, NMR, MS) data are fully consistent with the assigned structures. All known compounds were characterized by NMR and melting point. [b]Isolated yield. [c]Lit. m.p. 110-111 °C[9]. [d]In this case, CsF (3.0 eq) was used instead of 2M Na_2CO_3. [e]Lit. m.p. 122-123 °C[10]. [f]Lit. m.p. 83-85 °C[11]. [g]Lit. m.p. 126-128 °C[12]. [h]Lit. m.p. 88-89 °C[13]. [i]Lit. m.p. 85 °C[14].

A variety of aryl electrophiles were studied and the results are summarized in Table 1. As expected, the nature and substitution of the aryl halide had a strong influence on the cross-coupling reaction. In the case where an electron rich electrophile **A** was used, the electron rich boronate **D** generated *in situ* undergoes an efficient cross-coupling reaction with electron poor aryl electrophiles **B**. For example, the cross-coupling of *p*-iodoanisole **2** with *p*-bromochlorobenzene **3** afforded the coupled product **4** in 81% yield (Entry a). A similar result was obtained for the coupling reaction **2** with 3-bromoquinoline (**9**) (Entry f). However, a lower yield of 60% was obtained when the reaction was done in the reverse order (Entry b). Conversely, modest yields (41-50%) were obtained when both aryl halides were electron poor (Entries c-e). In these cases a substantial amount of homocoupling of the aryl halide **B** was observed. The cross-coupling of *p*-bromobenzaldehyde (**5**) with (**3**) under these conditions afforded the coupled product **6** in only 20% yield. However, replacing the base Na_2CO_3 by CsF provided the biaryl product **6** in 43% yield (Entry c).[15] The cross-coupling of the methyl ester **11** with bromobenzene (**12**) and 5-bromo-*m*-xylene (**14**), under these mild conditions afforded the coupled products **13** and **15** in high yields of 69% (Entry g) and 83% (Entry h), respectively.[16] The cross-coupling of 3-bromothiophene (**16**) with an electron rich halide **2** furnished the coupled product **17** in 80% yield (Entry i). Inverting the aryl halide addition sequence gives the biaryl **17** in a moderate yield of 34% (Entry j). Similarly, the cross-coupling reactions of 3-bromoquinoline (**9**) with 3-bromothiophene (**16**) gave moderate yields of 29-40% for the heterobiaryl **18** (Entries k-l). The lower yields in these cases could be attributed to the slow formation of the corresponding boronates and to competitive homocouplings. This method was shown not to be limited to aryl halides since phenyl triflate (**19**) coupled smoothly with *p*-iodoaniline (**2**) in yields ranging from 70-73% under these reaction conditions (Entries m-n).

A typical procedure for the cross-coupling is as follows: A flask charged with *p*-iodoanisole (**2**) (234 mg, 1.0 mmol), diborane **1** (279 mg, 1.1 mmol), KOAc (294 mg, 3.0 mmol) and $PdCl_2$(dppf) (24 mg, 0.03 mmol) was flushed with nitrogen. DMF (6 mL) was added and the reaction was stirred at 80 °C for 2 h. After cooling the solution to room temperature, *p*-bromochlorobenzene (**3**) (383 mg, 2.0 mmol), $PdCl_2$(dppf) (24 mg, 0.03 mmol) and 2M Na_2CO_3 (2.5 mL, 5.0 eq) were added and the mixture was stirred at 80 °C under nitrogen overnight. The solution was cooled to room temperature, the product was extracted with Et_2O (15 mL) and washed with H_2O (15 mL), brine and dried over $MgSO_4$. Finally, purification on silica gel using 5% ethyl acetate in hexane as the eluent gave 218 mg (81%) of 4- chloro-4'-methoxy-biphenyl (**4**).

In summary, we have developed a one pot reaction for the preparation of biaryls. This procedure avoids the isolation of boronic acids and is especially advantageous when base sensitive groups such as aldehydes, nitriles and esters are present. In addition, this *in situ* method should be equally applicable to alkenyl halides and alkenyl triflates.

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16. These isolated yields excludes the small amount of the corresponding acid detected in the crude reaction mixtures.

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